Guideline for Protecting Residents From Inhalation Exposure to Petroleum Vapors

State of Maine
Department of Environmental Protection
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Paper copies of the entire document may be reviewed at DEP Regional Offices

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Many individuals and organizations participated in the development of this Guideline. The "Residences Impacted by Petroleum Vapors Committee (RIPVC)," formed by the State of Maine Department of Environmental Protection, first recognized the need for and made important contributions to this guideline. We gratefully acknowledge the substantial contributions of the following RIPVC members (listed alphabetically):

- Sheryl J.M. Bernard, Oil and Hazardous Materials Specialist II, State of Maine, Department of Environmental Protection
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1. INTRODUCTION

Petroleum spills can adversely affect indoor air quality in homes, yet no comprehensive guidance is available to aid state agency staff in responding to this problem. The Maine Department of Environmental Protection (DEP) receives hundreds of calls each year from residents concerned about fuel oil spills, some of which create indoor air quality problems in homes. This Guideline describes DEP's approach for responding to residential indoor air quality concerns resulting from fuel oil, gasoline and kerosene releases during storage or delivery.

1.1 Background

Petroleum may affect residential indoor air quality following accidental releases from interior/exterior/underground oil heating systems as well as underground gasoline tanks and piping. Fuel oil and kerosene spills are commonly the result of storage system failures (corrosion of the copper line or tank), overfills and over-pressurization of the system, severed filters, tank rollovers due to unstable foundations, and delivery to incorrect locations. Gasoline spills usually result from corroded or improperly installed underground tanks or piping. Residential indoor air may be impacted by petroleum spilled in a residence, petroleum-contaminated groundwater migrating into a basement and volatilizing, or petroleum vapors entering a building.

Numerous variables affect the degree to which residents may be exposed to petroleum and the amount of risk they face. The magnitude of exposure and the ability to mitigate the exposure depends on factors such as:

- distance between the spill site and the residence
- time of year when the spill occurred
- duration of the spill
- time since the spill occurred
- amount of product spilled and recovered
- air exchange rate for the residence
- presence of a barrier between occupied spaces and petroleum-contaminated media
- foundation design (inclusive of sub-slab and perimeter drainage systems)
- amount of time residents spend in the affected area(s)
- type, design and operation of building HVAC system(s)
- roof and surface drainage systems
- hydrogeologic setting and meteorological conditions

All of these variables combine to create site specific and temporal exposure conditions that influence exposure in petroleum-contaminated homes.

1.2 Intent and Limitations of Guideline

DEP staff can use this Guideline to determine:

- when the risk posed by petroleum vapor warrants investigation;
- when the risk posed by petroleum vapor warrants evacuation;
- when indoor air quality monitoring is needed;
- when corrective action is needed;
- how the investigation should be conducted; and
- how indoor air quality data should be evaluated to ensure that the health of all residents is protected.

This Guideline addresses residential exposure to petroleum vapors via the inhalation route of exposure. It establishes indoor air concentration Action Levels for some petroleum constituents that are intended to guide decision-making regarding evacuation and cleanup. The Action Levels are protective of human health using the best toxicological data available at this time. They were established considering only potential human health effects; therefore, petroleum odors may persist for some time after these concentrations are reached. Nothing in this guidance is intended to address and protect against potentially explosive conditions associated with petroleum vapors. Please refer to DEP's Technical Services Leaking Underground Storage Tank (LUST) Procedural Guidelines, Indoor Vapor and Explosion Hazards section for information regarding hazardous atmospheres.

The intent of this Guideline is to assist DEP staff in responding to resident calls, not to dictate exactly what should be done in each case. DEP must implement this Guideline with some flexibility for several reasons:

- Over time, sampling and analytical methods likely will change and improve;
- As new toxicity data become available, the Action Levels should be reexamined; and
- Each home is different, requiring attention to site-specific influences on indoor air quality.

DEP staff and residents must recognize that the Action Levels are based on a limited set of available data and should be used judiciously. Also, the selection of indicator compounds depended on the adequacy of available petroleum product composition data, and, like the toxicity data, these data are limited. As more is learned about the toxicity and composition of gasoline, number 2 fuel oil and kerosene vapors, the Action Levels should be modified appropriately.

1.3 Organization of the Guideline

Section 2 provides practical instruction and information needed to implement the Guideline. Section 3 provides a health advisory on petroleum vapors that can be distributed to concerned residents. Appendices A through K include background information and data

used to develop the Guideline. To understand the basis for the Guideline and all of the recommendations incorporated into it, DEP staff need to read this document in its entirety, including all appendices.

2. STEP-BY-STEP INSTRUCTION FOR IMPLEMENTING THE GUIDELINE

Sections 2.1 through 2.8 outline the steps DEP should take in investigating petroleum spills that impact residential indoor air. This approach is based on (1) information in DEP records regarding residential contamination cases that have been investigated and remediated by Maine DEP staff; (2) ideas and comments received by members of the Residences Impacted By Petroleum Vapors Committee (RIPVC); and (3) results of research on sampling and analytical methods, petroleum compound background indoor air concentration data and available toxicity information.

2.1 Receive Call from Resident - Investigation Initiation

The investigation begins when a DEP staff member receives a telephone call from a Maine resident concerned about indoor air quality problems caused by a petroleum spill. The recipient of this call requests the caller's name and address as well as a description of the problem.

2.2 Conduct Interview and Visual Inspection

A member of DEP's Response Services inspects the residence to identify the petroleum spill, the type and quantity of petroleum and the extent of residential contamination. A petroleum spill may occur inside or outside of the residence. During this inspection, the DEP invesigator will first determine whether the petroleum spill is affecting or likely to affect indoor air quality. Use the "Residential Investigation Data Form" to describe the petroleum spill, the extent of residential contamination, any health effects, and general information about the residence and its occupants.

It is unlikely but possible that residents will call DEP regarding small spills (e.g. a small quantity of gasoline) that can either be cleaned readily or will rapidly evaporate, without significant impacts on indoor air quality. In these cases, extended remediation and indoor air sampling may not be warranted. If the petroleum spill is or has the potential to affect indoor air quality, DEP should proceed with the next steps in the Guideline.

2.3 Advise Residents and Make Recommendation Regarding Evacuation

During the initial visit to the residence, DEP staff will:

- Advise residents about insurance coverage;
- Provide residents with DEP's "Health Advisory on Indoor Petroleum Vapors;"
- Complete all parts of the "Residential Investigation Data Form;" and

- Advise residents to leave their home if they are experiencing discomfort or health effects associated with the petroleum. This advice is provided prior to obtaining any indoor air sampling results.

2.4 Conduct Appropriate Corrective Action and Collect a Baseline Indoor Air Sample

Conduct appropriate corrective action as soon as possible. The goal of corrective action is to to reduce the level of petroleum vapors in the house as quickly as possible. DEP staff will rely on PID samplers to locate source areas and to guide cleanup efforts. The home should be ventilated to the greatest extent possible during corrective action to speed reduction of indoor petroleum vapor concentrations. Refer to DEP Technical Services LUST Procedural Guidelines, Indoor Vapors and Explosive Hazards section.

Remediation takes precedence over indoor air quality sampling, and should occur as quickly as possible. However, DEP Technical Services should collect a time-weighted average baseline sample near the petroleum spill area (most likely the basement) at the earliest convenient time. Concentration data from this "source area" sample can be used to represent a conservative estimate of risk and can help DEP to evaluate whether corrective action measures are successful. Assuming that the source area is not located in a part of the home regularly used by residents, a second baseline sample should be collected in the main living area. This "living area" sample will provide a better estimate of the petroleum concentrations to which residents are exposed.

Each time DEP Technical Services collects an indoor air sample, the "Indoor Air Sampling Form" must be completed.

2.4.1 Indoor Air Sample Collection Protocol

Collection of time-integrated indoor air samples is required for evaluating longer-term (sub-chronic and chronic) health risks. A 24-hour sampling period is recommended, providing a somewhat better representation of exposure conditions than the instantaneous sampling. For the collection of these 24-hour time-integrated samples, we recommend the use of pre-evacuated SUMMA® passivated stainless steel canisters. Given ideal sampling conditions, SUMMA® canisters and solid absorbents such as Tenax™ have been shown to be nearly equivalent in terms of sensitivity and reproducibility. However, sampling conditions are nearly never ideal, and there are more potential sampling problems and interferences associated with solid absorbents than SUMMA® canisters. Sample breakthrough, blank contamination, and extraction efficiency are not concerns for sampling with SUMMA® canisters. SUMMA® canisters are very portable and easy to operate. In addition, because only a small portion of the total air sample is used for sample analysis, multiple analyses can be done for samples collected using SUMMA® canisters. Multiple analyses may be necessary for a variety of reasons including instrument failure, blank carryover, and sample confirmation. Tedlar bags are not recommended for time-integrated

samples because there is greater time for contact between the sample and the bag interior during longer-term sampling, which can potentially result in sample decomposition, artifact formation, and sample loss. SUMMA® canisters are a U.S. EPA validated sampling system, and the interior of SUMMA® canisters is specially treated to prevent sample decomposition and loss.

Indoor air sample collection protocols have been developed (US EPA 1993; CARB 1992) that address variables that might effect the success of sampling. These protocols were used in formulating the protocol for instantaneous indoor air sampling in Maine residences. The principal objective of baseline indoor air sampling is to obtain a worst-case representation of baseline conditions that provides a conservative indication of health risk. To obtain such a worst-case estimate, DEP must collect baseline samples under conditions expected to give rise to maximum indoor air concentrations. For example, worst-case sampling conditions may include (1) times of high groundwater levels with non-aqueous phase liquid (NAPL) and/or petroleum-contaminated water entering the home through a sump; or (2) soil vapor intrusion in winter when use of a heating system creates a chimney effect, drawing petroleum- contaminated vapors into the house.

Many variables can influence indoor air sampling results, including the air exchange rate for the house, operation of building HVAC system, hydrogeologic and meteorological conditions, and household activities and chemical use. All of these variables combine to create site-specific and temporal exposure conditions that must be considered in evaluating petroleum contamination in homes. To account for these variables, DEP should adhere to the following protocol for instantaneous indoor air sample collection:

- Place samplers where they will provide a representative sample of indoor air breathed by residents.
- Perform sampling in a room that is used regularly, such as a living room, den, or playroom.
- Avoid bedrooms, kitchens, and laundry rooms where use of personal products and other chemical products may interfere with sampling.
- Perform “living area” sampling at the lowest level of the house suitable for occupancy.
- Close windows and outside doors and keep them closed as much as possible during sampling, except for normal entry and exiting.
- Place indoor samplers on stands approximately 1 meter above the floor away from drafts (e.g., vents, open doors and windows, air conditioners, fans), high heat (heaters and heating vents), high humidity, exterior walls, and other obstructions to air flow.
- Samplers should be place on wooden stands or a piece of furniture in the central part of the room.
- All sampling equipment should be placed away from family traffic patterns and out of reach of pets and children.
- Do not operate fans or other ventilation equipment.

- Only operate air conditioning units that recirculate interior air.
- Samplers should not be placed close to attached garages, ash trays, or other possible petroleum constituent sources that might provide results that do not reflect contamination related to the petroleum spill.
- Remove or tightly seal obvious indoor sources of petroleum constituents during indoor air sampling; such as, fuels, paints, cleaning solvents, and mothballs.
- Document household conditions and activities during the sampling period using the "Indoor Air Sampling Data Form" in Appendix B.
- Document household characteristics, resident activities and potential ambient sources that may influence indoor air sampling results on "Residential Investigation Data Form."
- Sketch sampling locations.

Quality Control/Quality Assurance

- Follow the manufacturer's guidelines for use of sampling equipment and holding times.
- Collect field blanks and duplicate samples for at least 5% of houses investigated.
- Analyze samples as soon as possible after sampling.
- Do not ship sample bags by air unless cargo cabin is pressurized.
- Record general weather conditions during sampling, including ambient temperature.
- Maintain chain-of-custody forms.

2.4.2 Laboratory Analysis of Indoor Air Samples

All samples will be analyzed for the following analytes:

Benzene	Xylenes
n-Hexane	Naphthalene
n-Nonane	MTBE
Ethylbenzene	Volatile petroleum fractions: C_5 to C_8 aliphatics and aromatics; C_9 to C_{12} aliphatics and aromatics (when method becomes available)
Toluene	

The analytical method used by DEP must be able to identify and quantify certain indicator compounds as well as the volatile petroleum fractions. Both Ozone Precursor Analysis and GC/MS analysis (e.g., US EPA TO-14) have the capability of identifying and quantifying compounds in the volatile petroleum fractions. The validated compound list for the Ozone Precursor Analysis includes 75 hydrocarbon compounds, many of which are included within the volatile petroleum fractions. GC/MS analysis can also provide a more positive identification than the Ozone Precursor Analysis that uses a GC-FID detector because

compound fragment patterns, as well as retention times, can be used for identification. DEP continues to investigate analytical options for volatile petroleum fractions, including a method being developed by the Massachusetts Department of Environmental Protection.

2.5 Collect a Post-Corrective Action Indoor Air Sample

Following corrective action, DEP should collect a post-corrective indoor air sample to document reduction in indoor air petroleum vapors following DEP's remediation efforts. This sampling should occur soon after corrective action in both the "source area" and "living area." These samples should be collected in a manner that will provide a conservative estimate of exposure (i.e., sample when windows are closed). However, DEP investigators should be mindful that this sample may later form the basis of a decision to evacuate the residence if the concentration of petroleum vapor constituents exceeds Maine Action Levels established as part of this guideline.

2.6 Evaluate Indoor Air Sampling Results

The decision as to whether evacuation is needed will be based on a qualitative assessment of contamination levels and their impact on residents' health. If baseline sample results are available immediately, they may be used to decide whether evacuation is appropriate.

The post-corrective indoor air sample results should be compared with DEP's acute, subchronic and chronic concentration Action Levels listed in Table 1. Action Levels were established after considering possible residential background concentrations to ensure that evacuation or cleanup decisions are based solely on the petroleum spill.

TABLE 1
INDOOR AIR ACTION LEVELS
FOR PETROLEUM VAPORS IN RESIDENCES

Compound Name	Acute Action Levels		Subchronic Action Levels		Chronic Action Levels	
	ppb	µg/m^3	ppb	µg/m^3	ppb	µg/m^3
Benzene	50	160	19	60	3	10
Ethylbenzene	3,300	14,000	230	1,000	230	1,000
n-Hexane	*	*	108	400	57	200
Naphthalene	53	300	20	105	2	10
n-Nonane	*	*	1,000	5,300	100	500
Toluene	4,000	15,000	265	1,000	106	400
Xylenes	1,000	4,300	700	3,000	100	400

Notes:
* Insufficient data from which to derive an Action Level
µg/m^3 values are rounded to the nearest hundred

2.6.1 Human Health-Based Indoor Air Concentration Action Levels

The Action Levels are intended to protect sensitive individuals from significant health effects associated with inhalation exposures to compounds found in gasoline, kerosene, and fuel oil number 2. Sensitive individuals include pregnant women, young children, elderly people, individuals with compromised immune systems, and individuals in the general population who may be susceptible to the toxic effects of a chemical due to their genetic make-up. Three Action Levels are set for each petroleum indicator compound. The Action Levels are concentrations in air that, when exceeded in the living space, require additional sampling, remedial measures, and/or evacuation of the homes. The Action Levels represent protective levels for acute (1-14 days), subchronic (15 - 364 days), and chronic (365 days or more) exposure durations. All Action Levels are presented in Table 1 and derived in Appendix G.

In developing indoor air Action Levels for petroleum vapors, background concentrations of the indicator compounds were considered. It is not practical to implement an Action Level that is health protective but below the concentration considered to be background for indoor air in Maine homes. As presented in Appendix I of this guideline, there is considerable variability in the background concentrations of the indicator compounds in petroleum hydrocarbons in indoor air. None of these data are derived from residences in Maine, although the data collected from residences in Vermont are likely to be comparable. Therefore, the toxicity-based levels are compared with background concentrations taken from the Vermont data set. For compounds where there are no data from Vermont, the background data are taken from the USEPA TEAM database. Comparisons of the health protective levels and background concentrations are presented in Appendix G, Table 1. The Action Level for each indicator compound is the higher of the toxicity-based level or the background indoor air concentration.

2.6.1.1 Acute Action Levels

The acute Action Levels are based on short-term inhalation exposures to protect against acute and subacute health effects. DEP investigators may use them to decide whether evacuation is advisable. Acute exposures may be single or multiple events that do not exceed 14 days. The acute toxicity-based Action Levels are derived from studies in which animals or human were exposed to petroleum product vapors for relatively short periods of time; several hours up to 14 days. Data from lethality studies were examined (for comparative purposes) but not used in the derivation of the acute Action Levels. When possible, developmental and reproductive effects are considered since the Action Level is protective through a two-week period of time, although due to the nature of short-term toxicity studies, this information is not always available.

2.6.1.2 Subchronic Action Level

The subchronic Action Level is intended for use as a "re-occupancy" value during corrective action and apply to durations of 14 days through one year. They are derived from toxicological studies in which animals or humans were exposed to the vapors of compounds present in petroleum products for periods of time typically greater than two weeks, but less than a lifetime. The subchronic Action Level considers developmental and reproductive effects, in addition to other systemic effects. All of the toxicity-based levels exceed background residential concentration data.

2.6.1.3 Chronic Action Level

The chronic Action Levels are intended to protect sensitive individuals over the duration of a lifetime while residing in a single home. Air concentrations at or below chronic action levels are suitable for long-term occupancy of the residence (i.e. 70 years). The chronic toxicity-based levels are derived from studies in which animals or humans were exposed to compounds present in petroleum products for periods of time typically greater than several months to a lifetime exposure. The chronic Action Level considers developmental and reproductive effects, in addition to other systemic effects. DEP investigators should note that if smokers are present in the residence or if the residence is located near ambient petroleum sources, it may not be possible to attain some chronic Action Levels.

All of the chronic Action Levels exceed background residential concentration data with the exception of that for benzene. Therefore, the chronic Action Level for benzene is set at the background indoor air concentration most likely to be found in Maine residences. Investigators should be aware that no background indoor air concentration data are available from Maine residences, so it will be useful to collect such data during the Trial Period to be sure that the chronic Action Level for benzene is appropriate.

2.6.1.4 Relationship between Action Levels, Odor Thresholds, Background Indoor Air Concentrations, and Other Regulatory Guidelines

When a petroleum release occurs, the odors associated with the vapors can be quite strong since the odor thresholds of fuel oil #2 and gasoline are low. Appendix J includes odor thresholds for selected petroleum products and constituents. Each compound and mixture has a minimum and maximum odor threshold. The lower the minimum odor threshold, the easier it is to smell the compound. As presented in Figure 1, the minimum odor thresholds of the indicator compounds toluene, hexane, n-nonane, and naphthalene are higher than minimum odor thresholds for the mixture. Therefore, there are compounds present in the mixture that have lower odor thresholds (and can be smelled by the resident at lower levels) than the indicator compounds as represented in Figure 1.

Action Levels, minimum odor thresholds, and background indoor air concentrations of the indicator compounds are compared in Figure 2. All of the Action Levels for benzene and naphthalene are below their odor thresholds, and therefore the residents will not smell these compounds if the Action Levels are met. The acute Action Levels for ethylbenzene, toluene, and xylene are above their odor thresholds, and therefore residents may smell these compounds even if the acute Action Level is met. In conclusion, there may be odors present in the living space when there is no associated health risk.
The background indoor air concentrations are all below the Action Levels, with the exception of the chronic Action Level for benzene (Figure 3).

The Action Levels presented in this report are intended to protect all residents. Several agencies publish regulations and guidelines that are intended to be protective of other exposure scenarios, principally workplace exposures. Appendix K summarizes some of these regulations and guidelines. The Recommended Exposure Limits (RELs) published by NIOSH are time-weighted average concentrations for up to a 10-hour workday during a 40-hour workweek. The Permissible Exposure Limits (PELs) are time-weighted average concentrations that must not be exceeded during any 8-hour work shift of a 40-hour workweek. The Threshold Limit Values (TLVs) published by ACGIH are time-weighted average concentrations for a conventional 8-hour workday and a 40-hour workweek to which nearly all workers may be repeatedly exposed without adverse effect. These three occupational guidelines differ somewhat, even though they were derived for similar receptors and exposures. Because they were derived for the workplace, these values are not suitable for evaluating residential indoor air quality.

Appendix K also presents Spacecraft Maximum Allowable Concentrations (SMACs) which are derived for very specific short-term exposures. Like the RELs, PELs, and TLVs, the SMACs do not protect sensitive sub-populations and are not appropriate for evaluating residential indoor air quality.

2.6.2 Revisit Evacuation Decision

Based on the results of post-corrective action indoor air sampling, DEP should reconsider the need for evacuation. Any DEP recommendation to evacuate the residence should be based on two factors:

- residents are experiencing adverse health effects;
  and/or
- the indoor air concentration of any indicator compound exceeds its acute Action Level in an inhabited part of the residence.

The highest indoor air concentrations generally are found in the basement where spills often occur. Evacuation is not necessary if acute Action Levels are exceeded only in the basement, and residents can avoid using the basement. If any indoor air quality sampling results exceed acute Action Levels for any indicator compounds, DEP should recommend

evacuation, unless DEP has strong reason to believe that indoor air quality has improved substantially since the time the sample was collected.

2.6.3 Is More Corrective Action Needed?

If the post-corrective action indoor air sampling results are greater than any Action Level, DEP Response Services and Technical Services staff should conduct additional corrective action and sampling. If the post-corrective action indoor air sampling results do not exceed acute Action Levels, residents may remain in their homes. However, if subchronic or chronic Action Levels are exceeded, additional corrective action may be warranted.

If post-corrective action indoor air sampling results are less than all applicable Action Levels, DEP must confirm that indoor air concentrations are consistently less than the chronic Action Levels by collecting two 24-hour time-integrated indoor air samples. These samples should be collected at times and locations that will provide an indication of "worst-case" potential exposure conditions. DEP investigators should use the sampling protocol and their own judgment based on site-specific factors to ensure that the two samples represent likely worst-case exposure conditions.

These samples should be collected in areas of the home with the highest potential exposure that are likely to be used by residents. While residents may be able to avoid use of their basement during corrective action when petroleum constituent indoor air concentrations may be elevated, in the long run, residents need to be assured that it is safe to spend time in their basements. If both time-integrated samples are collected at different times near the source area (usually in the basement), results will provide a conservative estimate of exposure conditions in the main living area.

2.7 Site Closure: All Investigation and Corrective Action Objectives Satisfied

Before any residential investigation may be closed, two time-integrated indoor air samples must be collected with concentrations below all chronic Action Levels. Given the potential temporal variation in indoor air quality, this requirement ensures that investigations continue until indoor air concentrations of indicator compounds consistently fall below chronic Action Levels.

If DEP finds that it is infeasible to attain Action Levels within the timeframe specified by the decision framework, DEP investigators should consult with the Maine Department of Human Services (DHS) to evaluate site-specific factors that may be preventing attainment of these indoor air quality goals. There are two likely reasons that Action Levels may not be attainable:

- The Action Levels consider available residential background concentration data for indicator compounds, but these data are scarce and not specific to Maine residences; and

- The Action Levels were established to protect human health, but they do not consider the practical limitations of corrective action measures available to DEP.

These factors should be evaluated in discussions with DHS during the Trial Period.

2.8 Documentation of the Residential Response Action and Remediation

A file must be maintained for each residential investigation. Each time the residence is visited by DEP personnel, the visit as well as all activities during the visit must be documented. A final report should be prepared that, at a minimum, includes the following information:

- Residential Investigation Data Form
- Residential Indoor Air Sampling Log(s)
- Field Notes
- Sampling Equipment and Methods
- Analytical Methods
- Chain-of-Custody forms
- All indoor air concentration data for indicator compounds and volatile petroleum fractions
- All quality control sample results, including field blanks and duplicates
- Photographs and sketches of the house and sampling locations
- Description of corrective action and its efficiency and efficacy

3. HEALTH ADVISORY ON INDOOR PETROLEUM VAPORS

Kerosene, unleaded gasoline, and fuel oils or home-heating oils are petroleum products. They are each made up of mixtures of many different kinds of chemicals referred to as hydrocarbons. Some of these hydrocarbons evaporate easily and are released into the air as petroleum vapors. Petroleum vapors have strong odors associated with them. Other petroleum chemicals do not evaporate into the air as easily, but may still smell if they are in an enclosed space like a basement.

People who live near an area where petroleum has been spilled may come in contact with petroleum if it moves into groundwater used for household purposes or when petroleum vapors have entered the soil and then move into basements of nearby buildings. If there is a petroleum spill in your basement, or there are strong odors that seem to be due to petroleum, it is best to leave the basement or the room(s) where the odor is strongest.

How can an unleaded gasoline spill affect my health?

Health effects may occur from breathing unleaded gasoline vapors in the air. Many of the harmful effects seen following exposure to unleaded gasoline are due to the individual chemicals in the gasoline mixture. The kinds of health effects that may occur depend upon the amount of unleaded gasoline that has spilled, and the length of time the spill has been present. If unleaded gasoline was recently spilled and you have been breathing concentrated gasoline vapors in indoor air, which is where the highest levels of gasoline vapors are expected, you may begin to feel dizzy, nauseated or drowsy and you may develop a headache. At much higher concentrations, more serious health effects, such as coma or potentially even death, may occur.

What are the long-term effects that may result from being exposed to an unleaded gasoline spill?

The possibility of long-term health effects from breathing unleaded gasoline vapors depends upon the amount that has spilled and the length of time the spill has been present. There is little information regarding effects on developmental or reproductive effects in humans from breathing unleaded gasoline vapors, but some of the individual chemicals in the gasoline mixture are known to have reproductive or developmental effects. Scientists have not yet determined whether breathing unleaded gasoline vapors causes cancer in humans.

How can a kerosene spill affect my health?

Health effects may occur from breathing kerosene vapors in the air. The kinds of health effects that may occur depend upon the amount of kerosene that has spilled, and the length

of time the kerosene spill has been present. Breathing kerosene vapor for as short as one hour can make you nauseated, increase your blood pressure, or irritate your eyes. Breathing moderate amounts of kerosene may also slightly decrease your ability to smell. Breathing much higher concentrations of kerosene may cause headaches and poor coordination.

What are the long-term effects that may result from being exposed to a kerosene spill?

Kerosene has not yet been evaluated for its ability to cause cancer. It is not known whether kerosene can cause birth defects or affect reproduction.

How can a home heating oil (fuel oil # 2) spill affect my health?

Health effects may occur from breathing home heating oil vapors in the air. The kinds of health effects that may occur depend upon the amount of home heating oil that has spilled, and the length of time the oil spill has been present. Inhalation of number 2 fuel oil vapors may make you nauseated or dizzy. It may also give you a headache or make it difficult for you to concentrate.

What are the long-term effects that may result from being exposed to a home heating oil (number 2 fuel oil) spill?

The possibility of long-term health effects from breathing home heating oil vapors depends upon the amount that has spilled and the length of time the spill has been present. Breathing number 2 fuel oil vapors for a long time may cause you to be tired or anxious or to have mood swings. There is some indication that number 2 fuel oil might be associated with reproductive or developmental effects, but only limited information are available. It is not known whether breathing home heating oil vapors causes cancer in humans.

How do I know if my health is being affected by the petroleum (fuel oil/kerosene/gasoline) spill?

If you are experiencing any of the health effects that are described above, then your health may be affected by the petroleum spill. Elderly people, children, and people who are chronically ill may be at greater risk for health effects associated with petroleum products as compared to healthy adults.

What should I do if I am experiencing health effects from a petroleum spill?

It is important to leave any area where strong odors from petroleum vapors are present. Seek fresh air either outside or indoors by opening windows and/or doors. Opening windows in the basement should help to reduce strong odors caused by petroleum vapors.

If you continue to experience health effects associated with petroleum vapors, you should seek medical advice.

Do lingering petroleum vapor odors have health effects associated with them?

The nose is very sensitive to extremely low levels of petroleum products. Based on the information available, it is possible that odors may linger without any health effects. These odors are called nuisance odors since they do not appear to cause any health effects, but are unpleasant to smell.

What are Maine DEP's action levels?

The *acute action levels* protect against health effects resulting from short-term inhalation exposure (i.e. less than 14 days). DEP investigators may use these values to decide whether evacuation is advisable. The *subchronic action levels* are "re-occupancy" concentrations during corrective action and are applicable to exposure durations of 14 days up to one year. The *chronic action levels* protect sensitive individuals over the duration of a lifetime while residing in a single home. Air concentrations at or below chronic action levels are suitable for long-term occupancy of the residence (i.e. 70 years).

Where may I obtain more information?

If you have additional health related questions, call (207) 287-5189 to contact Doctor Andrew Smith, Director of the Environmental Toxicology Program at the Bureau of Health of the Department of Human Services. To report a petroleum release or request guidance for cleaning up spills, contact the Department of Environmental Protection, Bureau of Remediation, Division of Response Services at (800) 482-0777. If you want assistance in testing your indoor air quality, consult your local telephone directory for consultants who provide testing services.

4. FIGURES

Figure 1: Odor Thresholds of Petroleum Products and Constituents

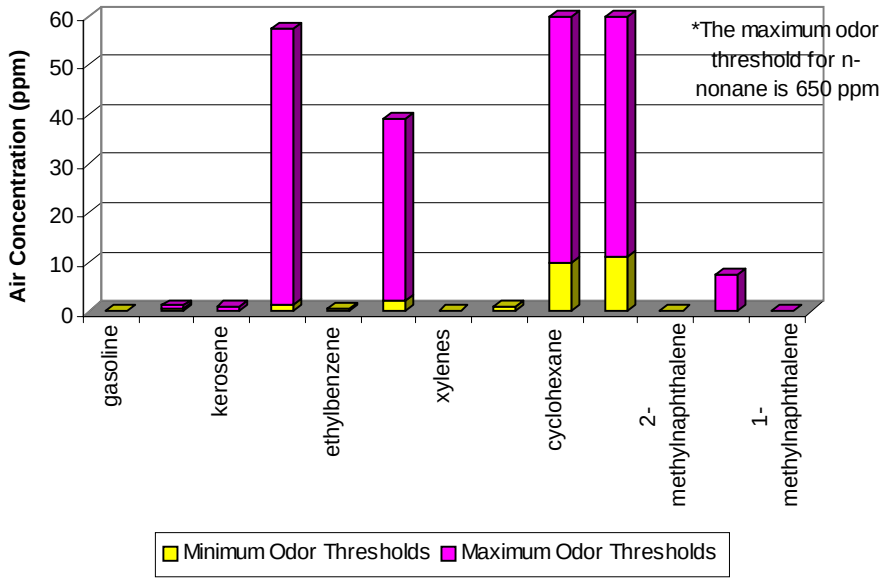


Figure 2: Comparison of Action Levels, Odor Thresholds and Background Air Concentrations

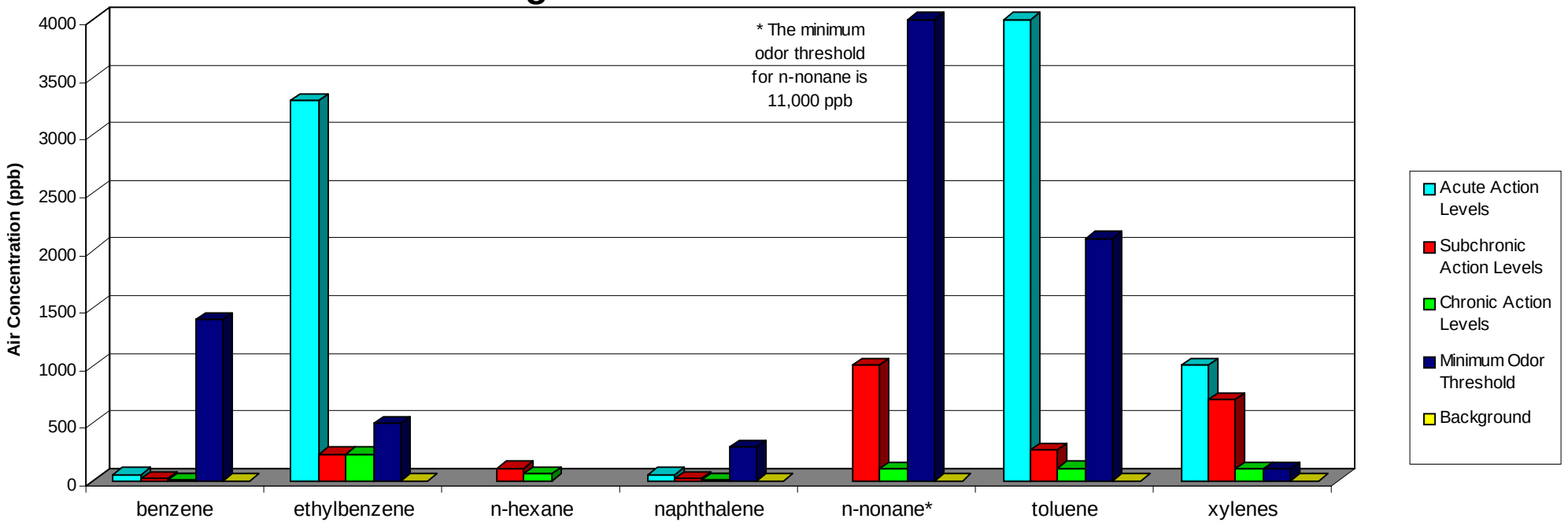
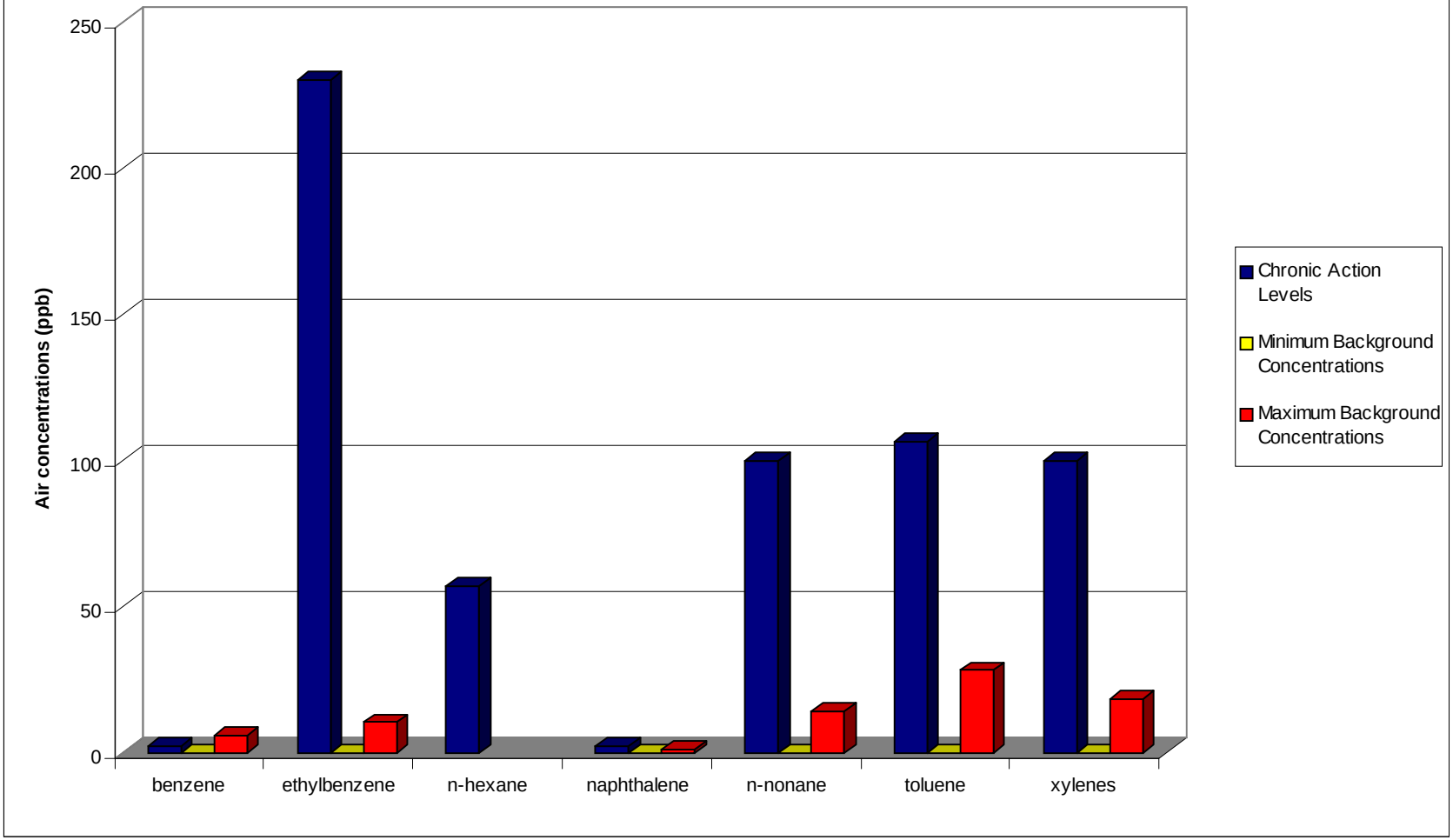


Figure 3: Comparison of Chronic Action Levels and Background Indoor Air Concentrations



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APPENDIX A - Glossary

GLOSSARY

Acute Action Levels – concentrations in air that, when exceeded in the living space for 1 to 14 days, require that additional sampling, remedial measures, and/or evacuation of the homes take place

Acute exposure – refers to an exposure of short duration (24 hours or less); often refers to a single exposure event

Adverse hematological effects – typically a reduction in the number of red blood cells, white blood cells, and platelets

Aliphatic compounds- straight-chain hydrocarbons

Alkanes – straight chain hydrocarbons that do not contain carbon-carbon double bonds

Alkenes - hydrocarbons that contain one or more carbon-carbon double bonds

Aplastic anemia – a form of anemia resulting from a failure of the bone marrow to produce adequate quantities of the essential blood components, including leukocytes and platelets

Aromatic compounds - ring or multiple ring chemical structures containing alternating single and double bonds

Ataxia - failure of muscular coordination; irregularity of muscular action

Background - means those levels of oil and hazardous material that would exist in the absence of the disposal site of concern which are:

(a) ubiquitous and consistently present in the environment at and in the vicinity of the disposal site of concern; and

(b) attributable to geologic or ecologic conditions, atmospheric deposition of industrial process or engine emissions, fill materials containing wood or coal ash, releases to groundwater from a public water system and/or petroleum residues that are incidental to the normal operation of motor vehicles

B-cells – cells that mature in the bone marrow and help to build antibodies

Bioassay – an experiment for estimating the nature, constitution, or potency of a chemical by means of the reaction that follows its application to living organisms or cells

Carcinogen – a cancer-causing agent

Cerebellar dysfunction – dysfunction of the cerebellum, which is the section of the brain that coordinates muscular movement

Chronic Action Levels – concentrations in air that, when exceeded in the living space for 365 days or more, require that additional sampling, remedial measures, and/or evacuation of the homes take place

Chronic exposure - multiple exposures occurring over an extended period of time or a significant fraction of the animal's or the individual's lifetime

Cycloalkanes - alkanes in which the carbon atoms form a ring

Delirium – a temporary state of extreme mental excitement, marked by restlessness, confused speech, and hallucinations

Developmental toxicity - any detrimental effect on developing organisms produced by exposures during embryonic stages of development

Edema – an abnormal accumulation of fluid in cells, tissues, or cavities of the body, resulting in swelling

Epidemiology - the study of the distribution and determinants of disease frequency in human populations

Metaplasia – abnormal change of one type of tissue into another

Exposure assessment – an appraisal of the magnitude of actual and/or potential human exposures, the frequency and duration of these exposures, and the pathways by which humans are potentially exposed

Epithelium – cellular tissue covering external body surfaces or lining internal surfaces

Erythrocytes – red blood cells

Extrapolation - an estimation of a numerical value of a function (for instance the effect of a chemical on human health) at a point outside the range of data used to calibrate the function (for instance data from animal studies)

Hematocrit - the percentage of red blood cell mass (volume) within whole blood

Hematopoietic – referring to the production of blood cells by the blood-forming organs

Hematuria – the presence of red blood cells in the urine

Hemoglobin - oxygen-carrying protein of the red blood cells

Hepatocellular adenoma or carcinoma – cancer of the liver

Hemolysis – the destruction of red blood cells

Hyperplasia – an abnormal increase in the number of cells composing a tissue or organ

Isomers - compounds having the same chemical formula but different structures

Leukocytes – white blood cells

Leukocytosis - a transient increase in the number of leukocytes in the blood, resulting from various causes, such as hemorrhage, fever, infection or inflammation

Leukopenia – a decrease below normal in the number of leukocytes in the blood

Mutagenesis – the production of irreversible changes in the genetic information stored in the DNA of living cells

Narcosis- a general, nonspecific, reversible mode of toxic action that can be produced in most living organisms by the presence of sufficient amounts of many organic chemicals; effects result from the general disruption of cellular activity and include depression of the cardiovascular system

Nasal turbinates – spiral-shaped, spongy bones in the nose

Neurological dysfunction – interruption of the normal function of the nervous system

Neurotoxic effects – adverse effects on the nervous system that produce symptoms including salivation, mild coordination loss, and fine tremors

NOAEL – the no-observed-adverse-effect-level, which is the highest dose level of a chemical that, in a given toxicity test, causes no observable adverse effect in the test animals

Nonpolar compounds - contain no polarized bonds or only polarized bonds in which the resulting charges are distributed symmetrically throughout the molecule

Olfactory – referring to the sense of smell

Organic compounds - compounds that contain carbon, usually in combination with elements such as hydrogen, oxygen, nitrogen and sulfur

Peripheral neuropathy – disease of the nervous system affecting nerves in the extremities

Qualitative - consisting of general observations about the system

Quantitative - comprising numbers obtained by various measurements of the system

Reference concentration (RfC) - an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure (typically measured as a mass of chemical per volume of air i.e. microgram per liter) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious non-cancer effects during a lifetime

Reference dose - an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure (typically measured as mass ratio of chemical to body weight) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious non-cancer effects during a lifetime

Renal disease - disease of the kidneys

Reticulocyte – a type of young red blood cell

Sertoli cells – cells found in the walls of the seminiferous tubules of the testis that anchor and nourish the developing sperm cells

Skewed - asymmetric; a skewed distribution of data means that if the data are plotted, one tail of the curve is drawn out more than the other and the mean and the median will not coincide

Subchronic Action Levels – concentrations in air that, when exceeded in the living space for 15 to 364 days, require that additional sampling, remedial measures, and/or evacuation of the homes take place

Subchronic exposure - multiple exposures or continuous exposure over a period of two weeks to 7 years

T-cells – cells that are involved in rejecting foreign tissue, regulating immunity, and controlling the production of antibodies

Teratogenic - causing malformations or birth defects as a result of exposure during embryonic or fetal development

Thrombocytes – blood cells that initiate the process of blood clotting

Thrombocytopenia – a reduction in the number of platelets in the blood, resulting in bleeding into the skin, spontaneous bruising, and prolonged bleeding after injury

Toxicity – the inherent potential of an agent to cause adverse effects in a living organism when the organism is exposed to it

Uncertainty Factor (UF) - means one or more factors, each generally one order of magnitude, by which a no-observed adverse-effect level is divided in accordance with EPA-approved method to reflect uncertainty in the various types of data used to estimate a Reference Dose or Reference Concentration

Volatilize - to convert all or part of a liquid or solid into vapor

Volatile organic compound - an organic compound with a boiling point less than 200 degrees Celsius

Weight-of-evidence assessment – an EPA classification system for characterizing the extent to which the available biomedical data indicate that an agent is a human carcinogen

APPENDIX B - Forms Used in Conducting Residential Investigations Under the Guideline

State of Maine Department Of Environmental Protection
RESIDENTIAL INVESTIGATION DATA FORM

Spill Number: _____

PART 1: RESIDENT INFORMATION

Resident's Name: _____

Address: _____

_____

Telephone number: _____

Primary language of residents (if not English): _____

OHMS Responding to spill: _____
First day of investigation: _____

****

PART 2: CHARACTERIZE PETROLEUM SPILL

1. What type of petroleum product was spilled?
   ☐ fuel oil ☐ gas ☐ kerosene ☐ other _____

2. How much product was released (gallons)? _____ and how much recovered (gallons)? _____

3. When did the petroleum spill occur?

_____

_____

4. How did the petroleum spill occur?

_____

_____

_____

_____

5. Where did petroleum spill occur? Describe all locations within the home impacted by the spill.

_____

PART 3: HEALTH EFFECTS ASSESSMENT

6. Are residents complaining of any health effects attributable to the spill? ☐ YES ☐ NO

IF YES, complete the following table:

	Have household members experienced this health effect since the petroleum spill?	
SYMPTOM	**YES**	**NO**
runny nose		
eye irritation		
nausea		
confusion		
diarrhea		
stomach cramps		
coughing		
dizziness		
throat irritation		
drowsiness		
headache		
difficulty concentrating		
poor coordination		

Additional comments regarding health effects:

_____

_____

_____

****

PART 4: GENERAL HOUSEHOLD INFORMATION

7. Which best describes the home? (Check all that apply.)
   _____ one-family house detached from other houses
   _____ one-family house attached to one or more houses

_____ building for 2 or 3 families
_____ building for 5 or more families
_____ first floor
_____ second floor
_____ third floor

8. Is there an attached garage? ☐ YES ☐ NO

9. Which of the following does the home have?
____ basement ____ basement and crawlspace
____ crawlspace ____ other(specify)
____ slab foundation ____ don't know

10. Does the foundation/slab have a drainage system? _____. If yes, please describe_____
_____.

11. Approximately when was the home built?
____ 1986 or later ____ 1950-1959
____ 1980-1985 ____ 1940-1949
____ 1970-1979 ____ 1939 or earlier
____ 1960-1969 ____ don't know

12. Has the home undergone any recent (previous year) renovations? ☐ YES ☐ NO

IF YES, please describe any renovations:

_____

_____

_____

13. Who else lives at this home?

	Age	Sex
_____	___	___
_____	___	___
_____	___	___
_____	___	___
_____	___	___

14. Outdoor area around the home includes:
____ yard with lawn, trees and/or shrubs
____ yard without lawn, trees and/or shrubs
____ other (e.g. garden)_____

15. Describe the amount of vehicle traffic passing in front of or near the home?
    ____ heavy highway traffic ____ quiet, paved street
    ____ busy, paved street ____ dirt road
    ____ moderately-busy, paved street

16. Are there any potential outdoor sources of petroleum (e.g. gas stations, parking lots, marinas) near the home (within about a mile)? ☐ YES ☐ NO

IF YES, what types of sources?

Source	**Yes**	**No**
Gas station or other fuel sources		
Parking lots		
Heavy traffic		
Other (describe:_____)		

****

PART 5: HEATING/AIR CONDITIONING/AIR CLEANING?

17. How is the home heated? (Mark all that apply)
    ____ Electricity ____ Natural gas ____ Other
    ____ Kerosene ____ Propane gas
    ____ Solar ____ Oil
    ____ Coal ____ Wood (fireplace, wood stove)

18. Is the home heated by any type of furnace system? (Mark all that apply.)
    ____ No
    ____ Steam or hot water furnace system (radiators or baseboards)
    ____ Central warm air furnace with ducts to rooms
    ____ Vented floor, wall or pipeless furnace
    ____ Unvented floor, wall or pipeless furnace

19. Identify any secondary heating systems used in the home, including frequency of use.
    ____ wood stove
    ____ space heaters (specify electric, kerosene, oil) _____
    ____ fireplace
    ____ coal stove

20. Do residents use a gas cooking stove? _____

21. Do residents use any air cleaning devices? Do not count furnace filters. (Mark all that apply.)
    ____ None ____ Yes, charcoal

____ Yes, filter ____ Yes, electrostatic precipitator
____ Yes, ion generator ____ Yes, other (specify) _____

22. Does the home have any air conditioning? ☐ YES ☐ NO
IF NO, skip to question # 22.

Which rooms have air-conditioning? (Mark all that apply.)
____ all rooms (central air conditioning)
____ living or family room
____ bedroom
____ other rooms (specify) _____

What type of air conditioning?
____ Refrigerative ____ Both ____ Attic Fan
____ Evaporative ____ Don't know

Does the air conditioner recirculate indoor air, or bring in fresh air from outside, or both?
____ recirculates indoor air ____ both
____ brings in outside air ____ Don't know

****

PART 6: SMOKING

23. Does anyone living at this address smoke cigarettes, pipes or cigars? ☐ YES ☐ NO
IF YES, what is the total number of smokers in your household?____

24. About how many cigarettes are smoked on average per day inside the home?
____ fewer than 10 ____ 1 pack
____ 10 to 14 ____ 1 1/2 packs
____ 15 to 24 ____ 2 packs
____ 25 to 34 ____ 2 1/2 packs
____ 35 to 44 ____ 3 packs
____ 45 or more____ more than 3 packs

25. Not counting people living in the household, does anyone smoke cigarettes within the home? (Include regular visitors such as grandparents or babysitters.) ☐ YES ☐ NO

IF YES, counting only these other smokers, about how many cigarettes are smoked per day inside the home?
____ fewer than 10 ____ 1 pack
____ 10 to 14 ____ 1 1/2 packs
____ 15 to 24 ____ 2 packs
____ 25 to 34 ____ 2 1/2 packs
____ 35 to 44 ____ 3 packs
____ 45 or more____ more than 3 packs

26. Does anyone in the household smoke pipes or cigars?
____ pipes ____ cigars ____ neither

****

PART 7: POTENTIAL INDOOR SOURCES OF PETROLEUM PRODUCTS AND PETROLEUM COMPOUNDS

27. Conduct survey of likely indoor sources of petroleum products and petroleum constituents and complete the following table:

Potential Indoor Sources	Is source present in home?		Location (i.e. room)
	Yes	No	
Open[1] containers of paint and paint thinners			
Open containers of any petroleum products			
Cleaning or furniture refinishing solvents			
mothballs			
Oil tanks			
Wood stoves			
1 "open" is defined as a container that has been opened, even though it may not be open at the time of the investigation.			

State of Maine Department Of Environmental Protection
INDOOR AIR SAMPLING FORM

Resident's Name: _____

DEP Investigator: _____

Sample Collection Date: ____/____/____

Sampling Equipment: _____

Was there an odor present in the home at the time of sampling? ☐ YES ☐ NO

If yes, describe the odor. _____

Part A: TIME-INTEGRATED INDOOR AIR SAMPLE INFORMATION

Sample Type		Sample Number	Sampling Period		Describe sampler location
Source Area	Living Area		Start (hr:min)	Finish (hr:min)	

Part B: HOUSEHOLD ACTIVITIES THAT OCCURRED WHILE THE INDOOR AIR SAMPLERS WERE OPERATING

(1) Were any cigarettes, cigars or pipes smoked in the home? ____YES ____NO

If YES, how many cigarettes or cigars were smoked or for how long was the pipe smoked?

_____ number of cigarettes
_____ number of cigars
_____ duration of pipe smoking (hours)

(2) Did residents use any pesticides, household cleaning products, or other household chemical products? ___ YES ____ NO

If YES, identify all cleaners used and in which rooms:

Cleaner Type	Room

(3) Were any windows or doors open (other than normal opening and closing of doors as residents enter and leave the home)? ____ YES ____ NO

If YES, identify the rooms in which windows or doors were open and for how long:

Room	Number of windows open	For how long? (in hours)

(4) Was the home heated in any way? ____ YES ____ NO

If YES, what type of heating source was used (e.g. central gas, oil or electric heater, fireplace, woodstove, space heaters) and for how long?

_____
_____

(5) Did residents do any carpentry work or other hobbies? ____ YES ____ NO

If YES, please describe these activities

_____

_____

(6) Did residents perform any car maintenance in an attached garage? ___ YES ___ NO

If YES, please describe maintenance work

_____

_____

Part C WEATHER CONDITIONS DURING INDOOR AIR SAMPLING

1) Average outdoor air temperature (in degrees Celsius) _____

2) Prevailing wind direction W SW NW E SE NE N S

3) Average wind speed (km/hr) _____

4) Average relative humidity (%) _____

5) Average barometric pressure (inches of Hg) _____

6) Describe general weather conditions (e.g. sunny, cloudy)
_____

APPENDIX C - Selection of Indoor Air Analytes

SELECTION OF INDOOR AIR ANALYTES

It would not be practical to analyze indoor air samples for all possible petroleum constituents. Analytical and computational requirements would be excessive and cost-prohibitive. Even if concentration data were obtained for all petroleum constituents, the toxicity data and fate and transport data needed for assessing human health risk are not available for each constituent. For these reasons, DEP considered whether human health toxicity should be evaluated on the basis of whole petroleum products (i.e. gasoline, number 2 fuel oil and kerosene), on groupings, or fractions, of similar petroleum constituents (i.e. C_5 to C_8 aliphatics), or on individual constituents, or indicator compounds. With the whole product method, toxicity criteria for unweathered whole products are applied to the petroleum mixture found at a contaminated site. With the indicator method, the toxicity of the petroleum mixture is described by the toxicity of one or more individual petroleum constituents. The fraction method involves dividing petroleum constituents into carbon number range fractions that are each assigned a representative toxicity criterion.

To develop indoor air Action Levels for petroleum releases for the protection of human health, the scientific literature and approaches used by other regulatory agencies were reviewed. The literature review included searches of the National Library of Medicine's databases: *Medline*, *Toxline*, *Toxnet*, (searches focused on petroleum hydrocarbons and specific compounds present in kerosene, gasoline, and fuel oils).

To present inhalation risk to residents, a petroleum compound must be present in the spilled product, volatile, and toxic. To facilitate the selection of petroleum compounds for the evaluation of acute, subchronic, and chronic health effects from petroleum vapor exposure, tables were prepared summarizing the weight composition, vapor pressure, and toxicity of constituents of gasoline, number 2 fuel oil and kerosene (See Tables C-1a through C-3b). Based on these data, DEP selected several petroleum constituents as indicator compounds to assess indoor air quality in residences: benzene, toluene, ethylbenzene, xylenes, n-hexane, n-nonane, and naphthalene. Historically, such indicator constituents have been used adequately to evaluate cancer risk. However, they represent only a small part of petroleum products, and some groups are now developing petroleum fraction-based approaches to evaluate non-cancer risk. To ensure that it accounts for most of the risk associated with petroleum vapors, DEP should take advantage of these approaches and measure volatile petroleum fractions in addition to the indicator consituents.

Two groups have identified petroleum fractions: the Massachusetts Department of Environmental Protection (MADEP) and the Total Petroleum Hydrocarbon Criteria Working Group (the "Working Group"). Fractions identified by these two groups cover every type of petroleum product, not just kerosene, gasoline, and number 2 fuel oil. Since this Guideline addresses risk due to petroleum vapors, DEP should measure the following most volatile fractions:

Petroleum Hydrocarbon Fractions
C_5 to C_8 Aliphatics
C_5 to C_8 Aromatics
C_9 to C_{12} Aliphatics
C_9 to C_{12} Aromatics

MTBE is found in gasoline. Given its relatively high volatility, MTBE may affect indoor air quality in homes impacted by gasoline spills. It was not selected as an indicator compound because the benzene in gasoline is more volatile and toxic than MTBE and would therefore drive remedial actions. However, MTBE should be measured during the trial period to determine how important it might be for homes impacted by gasoline spills.

APPENDIX D - Summary of Petroleum Fraction-Based Approaches to Evaluating Non-Cancer Risk

SUMMARY OF PETROLEUM FRACTION-BASED APPROACHES TO EVALUATING NON-CANCER RISK

Introduction

This appendix provides a brief explanation of the use of petroleum fraction based approaches for evaluating non-cancer risk. Two groups have separately developed fraction based approaches: The Total Petroleum Hydrocarbon Working Group (TPHCWG) and the Massachusetts Department of Environmental Protection (MADEP).

Historically, environmental scientists and engineers have used various analytical techniques to measure Total Petroleum Hydrocarbons (TPH) in environmental media. These techniques, although useful for setting discharge limits in NPDES programs or delineating the extent of soil contamination, suffer from several disadvantages in a risk-based decision making framework. In particular:

- TPH analysis is non-specific and neither recognizes nor incorporates the diversity of constituents found within and among the various petroleum hydrocarbon products;

- It is not possible to assign toxicity factors to total petroleum hydrocarbons or even to a known type of whole petroleum product such as fuel oil;

- TPH analysis does not reflect weathering of the petroleum product likely to occur in environmental media.

This last point is important in risk assessment. After release to the environment, the composition of petroleum products change over time and space due to differential partitioning and weathering. (The term “weathering” generally refers to environmental degradation processes such as photolysis and microbial action).

The risk assessor then is left with the overwhelming task of either trying to develop toxicity factors for TPH (or large subsets such as gasoline or fuel oil), or to measure each constituent which may occur with TPH, and developing toxicity criteria for each compound. The first approach is impractical given the diversity of products and their diverse individual compositions. The second approach is cumbersome, expensive, and requires considerable research to develop a toxicity factor for each potential constituent.

General Approach

Therefore, groups assessing this problem have turned toward a petroleum fraction based approach. Essentially, this approach:

- divides the petroleum product into specific carbon ranges usually based on similar fate and transport characteristics or similar chemical properties;
- measures the total concentration of carbon compounds within those ranges;
- assigns toxicity factors to each range on the basis of a specific compound within that range for which adequate toxicity information exists; and
- measures the concentration of a selected group of compounds to assess cancer risk separately.

Advantages of the Fraction Based Approach

The fraction based approach overcomes the problems encountered with measuring TPH and attempts to recognize the diversity of constituents associated with various petroleum products. There are obvious advantages. Use of fractions:

- accounts for the partitioning and environmental weathering of spilled product;
- addresses any type of petroleum contamination regardless of whether one or more petroleum products were released to the environment because the fractions are defined by carbon number ranges rather than product type;.
- represents a practical alternative to evaluating hundreds of individual petroleum constituents that would be prohibitively expensive and unnecessary to evaluate risk.

TPHCWG Fraction and Analytical Method

The petroleum fractions developed by the TPHCWG are listed in Table 1. The TPHCWG's method for analyzing these fractions will soon by published by the TPHCWG in Volume 6 "Development of Fraction-Specific Toxicity Criteria for Total Petroleum Hydrocarbon (TPH)" (Rhodes et al. 1997).

This method reports analytical data by petroleum hydrocarbon fractions with segregation between aliphatics and aromatics (Rhodes et al. 1997). The analytical approach is a gas chromatographic method specifically modified to measure the concentration in soil of petroleum hydrocarbons corresponding to a hydrocarbon range from n-hexane (C_6) to n-octacosane (C_{28}), and a boiling point range of approximately 65°C to 450°C. It is based on

SW-846 EPA Method 3611 (Alumina Column Cleanup and Separation of Petroleum Wastes) and *SW-846 EPA Method 3630* (Silica Gel Cleanup) which are used to fractionate petroleum-derived mixtures into aliphatic and aromatic fractions. This method has been specifically designed to resolve and quantify thirteen aliphatic and aromatic fate and transport fractions previously selected by the TPHCWG.

Table 1
TPH Fractions Derived from Fate and Transport Characteristics and Associated Properties
(Based on an Equivalent Carbon Number Index[1])

	Solubility (mg/l)	Vapor Pressure (atm)	log Koc (c/c)	PF[2] (soil/water)	PF (soil/vapor)
Aliphatic Fractions					
C5-C6	3E+01	4E-01	2.8E+00	1E+01	3E-01
>C6-C8	5E+00	6E-02	3.5E+00	4E+01	9E-01
>C8-C10	4E-01	6E-03	4.5E+00	3E+02	6E+00
>C10-C12	3E-02	5E-04	5.4E+00	3E+03	5E+01
>C12-C16	7E-04	3E-05	6.9+E00	7E+04	1E+03
>C16-C21	2E-06	8E-07	9.0E+00	1E+07	1E+05
Aromatic Fractions					
C5-C7 (Benzene)	2E+03	1E-01	1.9E+00	9E-01	4E+00
>C7-C8 (Toluene)	5E+02	4E-02	2.4E+00	2E+00	9E+00
>C8-C10	6E+01	6E-03	3.2E+00	2E+01	5E+01
>C10-C12	2E+01	5E-04	3.4E+00	2E+01	2E+02
>C12-C16	6E+00	3E-05	3.7E+00	5E+01	2E+03
>C16-C21	7E-01	8E-07	4.1E+00	1E+02	4E+04
>C21-C35	7E-03	3E-10	5.0E+00	1E+03	3E+07

[1] Equivalent carbon number as defined in Gustafson et al. 1997
[2] PF - partition factors for soil to water and soil to vapor concentrations at equilibrium
Source: Total Petroleum Hydrocarbon Criteria Working Group, Volume 3, 1997

TPHCWG Toxicity Factors

The TPHCWG also assigned toxicity criteria to each fraction by selecting toxicity data most representative of the fraction from the toxicology literature on whole products, mixtures and individual petroleum constituents. When paired with the Working Group toxicity criteria, the fate and transport fraction data can be used to assess human health risk associated with exposures to petroleum-contaminated environmental media.

Massachusetts EPH/VPH Approach

MADEP published a regulatory framework for evaluating TPH in human health risk assessments (MADEP, 1994; MADEP, 1996). This framework recommends the EPH/VPH analytical procedure for petroleum hydrocarbon mixtures which consists of three steps: quantification of volatile petroleum hydrocarbons (VPH) and quantification of extractable petroleum hydrocarbons (EPH), and measurement of target analytes.

MADEP Analytical Method

The VPH method includes the following target analytes: benzene, toluene, ethylbenzene, and total xylenes (BTEX) as well as naphthalene and MTBE; alkanes/cycloalkanes in the C_5 to C_8 and C_9 to C_{12} carbon ranges; and aromatics/alkenes in the C_9 to C_{10} carbon range. The EPH method includes the following analytes: polycyclic aromatic hydrocarbons (PAHs); alkanes/cycloalkanes in the C_9 to C_{18} and C_{19} to C_{36} carbon range; and aromatics/alkenes in the C_{10} to C_{22} carbon range.

The VPH methodology calls for gas chromatography with a PID and FID in series. GC/PID is recommended for separation and detection of the VPH target analytes and the C_9 to C_{10} aromatic fraction, and the FID is used to detect the C_5 to C_8 and C_9 to C_{12} aliphatic fractions. For the EPH fraction, the sample extract is divided into aliphatic and aromatic fractions. GC/FID is used as the detector following concentration.

MADEP Toxicity Factors

MADEP developed the EPH/VPH methodology for specific application in human health risk assessment. Similar to the TPHCWG fate and transport fractions, MADEP assigned toxicity criteria to the fractions based on reference compounds selected to represent each fraction. MADEP promulgated cleanup standards for the EPH/VPH fractions based on the toxicity of the reference compounds, and the state has recommended the use of either or both EPH and VPH analysis for a variety of petroleum mixtures.

References

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APPENDIX E - Indoor Air Sampling and Laboratory Analytical Methods

INDOOR AIR SAMPLING METHODS

Many techniques are now available for the sampling and measurement of volatile organic compounds (VOCs) in indoor air. Both portable and stationary monitors are commonly used to sample indoor air. Sampling equipment is available to collect grab (instantaneous) samples and time-integrated samples. Real-time data can also be obtained using portable instruments but at the cost of high detection limits and non-specificity. Both active and passive sampling equipment are available. Active samplers typically utilize calibrated pumps to draw air into collectors or sensors, while passive samplers rely on simple diffusion of vapors into collectors or sensors.

Because an abundance of sampling equipment is available, careful decisions need to be made regarding which method is appropriate for a given situation. What method is appropriate for a given situation depends on several factors including the nature of the VOCs of interest, environmental conditions and the sampling objective. The target analytes in this Guideline are nonpolar organic compounds, and we need to detect specific compounds as well as summed fractions of compounds. For residential indoor air, environmental conditions of concern include building characteristics, temperature, humidity and ventilation. Sampling methods should be appropriate for the living spaces as well as the basements of residences.

The sampling goals for this Guideline include:

- estimate indoor air concentrations of selected petroleum compounds and fractions;
- provide the basis for evacuation recommendations;
- provide the basis for re-occupancy and long term health and safety recommendations; and
- aid in the identification of contaminant sources and the extent of contamination.

Based on these sampling objectives, we considered several criteria in the evaluation of sampling methods including:

- sensitivity;
- specificity (e.g., total vapors concentration versus chemical-specific concentrations);
- data quality (e.g., accuracy and reproducibility);
- response time;
- probability of interferences and false positives;
- technical feasibility (e.g., portability in the field and ease of use); and
- economic feasibility.

Sampling methods have been developed for different sampling objectives and hence certain methods are more appropriate than others with respect to the above criteria. The following sections describe common sampling methods in terms of these criteria. Table E-1 summarizes this information. Both the text and table separate field screening methods from methods requiring laboratory analysis. Because sampling methods are intricately tied into analytical methods, the table shows information on both sampling and analytical methods.

Information on sampling methods for indoor air assessment was obtained from several different sources. Literature searches and internet searches were conducted. U.S. EPA documents and information clearinghouses were consulted, in particular those of the Environmental Response Team (ERT), to determine which methods are recognized and used by U.S. EPA. Telephone interviews were held with several researchers in U.S. EPA, industry, state agencies, and academia who are actively involved in indoor air monitoring of volatile and semi-volatile compounds. Two full-service air quality laboratories (Air Toxics, Ltd., Folsom California; and Performance Analytical, Inc., Canoga Park, California) were consulted regarding the feasibility and cost of various sampling equipment and analytical methods. In addition, several instrument rental companies (Hazco, Valley Forge, Pennsylvania; CAE Instrument Rental, Palatine, Illinois; and Quantum Analytics, Inc., Foster City, California) were consulted to obtain information on model availability, model specifications and cost of current rental equipment.

Evaluation of Sampling Methods

This section provides detailed information regarding different sampling methods, their suitability for screening-level measurements and their approximate costs.

Field Screening Methods

Portable PID/FID Instruments

Portable PID/FID instruments have traditionally been used as general survey instruments at hazardous waste sites. These hand-held instruments employ either a photoionization detector (PID) or a flame-ionization detector (FID) for detection of vapors/gases. These portable instruments traditionally have been used during site investigations at hazardous waste sites, in particular for headspace analysis of soil and groundwater samples. Due to their widespread use in environmental response at hazardous waste sites, portable PID/FID instruments have also been used in responding to situations where petroleum vapors impact indoor air.

Table E-1
Summary of Sampling and Analytical Methodologies for Petroleum Vapors in Indoor Air

Method Name	Sample Media/ Field Instruments	Detector	Approximate Cost (per sample)	Typical Detection Limits	Comments: Rapid Response	Quantitative Analysis	Compound-specific Analysis	Hydrocarbon Fraction Data Reported	Time-integrated Samples	Probability of False Positives/False Negatives
Field Screening Methods										
Portable GC	Photovac 10S10, 10S50, 10S70 Models; HNU Systems Model 321 GC	PID (9.5, 10.2, and 11.7 eV lamps)	Instrument/ maintenance/ calibration	<5 ppb for known analytes	Immediate	Yes	Yes	No	Yes (although typically grab only)	Low (dependent on skilled calibration and data interpretation)
Portable PID/FID Instrument	Century Organic Vapor Analyzer (OVA)	FID	Instrument/ maintenance/ calibration	~0.2 ppm	Immediate	Semi	No	No	No (grab only)	Medium (detects methane, environment-sensitive)
	Photovac Micro Tip Models	PID (9.5, 10.2, and 11.7 eV lamps)	Instrument/ maintenance/ calibration	~0.2 ppm	Immediate	Semi	No	No (can be be insensitive to small-chained alkanes)	No (grab only)	High (sensitive to humidity, dust, power lines, transformers, or other radio wave transmitters)
	HNU Systems, Inc. PI-101, ISPI-101, and HW-101 Models	PID (10.2 and 11.7 eV lamps)	Instrument/ maintenance/ calibration	~1 ppm	Immediate	Semi	No	No	No (grab only)	High (same reasons as for Photovac Micro Tip)
Colorimetric Devices	Dräger Chip Measurement System	Substance-specific Chips	Instrument/ maintenance/ calibration	down to 0.2 ppm (benzene)	Immediate	Semi	Yes (one compound per chip)	No	No	Medium (humidity sensitive, potential interference)
	Colorimetric Tubes	Color change	pump kit/tubes (~$5 each)	down to 0.5 ppm (benzene)	Immediate	Semi	Yes (one compound per tube)	No	No	High (humidity sensitive, cross-sensitive to similar compounds)

Method Name	Sample Media/ Field Instruments	Detector	Approximate Cost (per sample)	Typical Detection Limits	Comments: Rapid Response	Quantitative Analysis	Compound-specific Analysis	Hydrocarbon Fraction Data Reported	Time-integrated Samples	Probability of False Positives/False Negatives
Methods Requiring Laboratory Analyses										
EPA Method TO-1	Tenaxâ Absorbent Cartridges	GC/MS	sample media ($20)/laboratory costs ($175)a,b	<1 ppb	Several days (with added cost)	Yes	Yes (extensive list of validated compounds)	Maybe (can be done upon request)	Yes	Low to Medium (detectable blank levels of BTEX on unused cartridges, potential breakthrough)
EPA Method TO-2	Carbon Molecular Sieves	GC/MS	sample media ($45) /laboratory costs ($175)a,b	<1 ppb	Several days (with added cost)	Yes	Yes (extensive list of validated compounds)	Maybe (can be done upon request)	Yes	Low to Medium (incomplete desorption)
EPA Method TO-3 (Boiling Point Distribution Analysis)	SUMMAâ Stainless Steel Canisters, Tedlar Bags	GC-PID/FID	sample media ($15)/laboratory costs ($150)a,b	~1 ppb for BTEX; ~10 ppb for TPH fractions	Several days (with added cost)	Yes	Yes (BTEX only)	Yes (calibrated for either gasoline or jet fuel)	Yes	Low
EPA Method TO-14	SUMMAâ Stainless Steel Canisters	GC/MS	sample media ($50)/flow controller ($20)/laboratory costs ($175)a	< 1 ppb	Several days (with added cost)	Yes	Yes (extensive list of validated compounds)	Maybe (can be done upon request)	Yes	Low
Analysis of Ozone Precursors	SUMMAâ Stainless Steel Canisters	GC-FID	sample media ($50)/flow controller ($20)/laboratory costs ($175)	~ 1 ppb	Several days (with added cost)	Yes	Yes (list of ~80 aliphatic and aromatic hydrocarbons)	Yes	Yes	Low
	Tedlar Bags		sample media ($15)/laboratory costs (		No					

a laboratory analytical costs are reported for a subset (5-10 chemicals) of the laboratory-validated compound list

b does not include the cost of a personal air sampling pump

Both PID and FID instruments are nonspecific detectors that measure total vapor/gas concentrations in air. A PID utilizes an ultraviolet (UV) lamp to emit photons. Vapors with ionization potentials less than that of the source lamp can be detected when positive ions form upon absorption of photons and current is produced. The current is converted to a concentration and is directly displayed on a meter or LCD display for the user. The strength of the UV lamp is a critical parameter with regard to the sensitivity of a PID instrument because only gases with ionization potentials near to or less than that of the lamp will be ionized, detected and measured by the analyzer. Energies of commonly used environmental probes are 9.5, 10.6, and 11.7 eV, and all three of these probes can detect many aromatic and large molecular hydrocarbons. The 10.2 and 11.7 eV probes can also detect some smaller organic molecules including smaller-chained aliphatic hydrocarbons. Due to their high ionization potentials (which range from about 12 to 16 eV), ambient air gases (e.g., O_2, N_2, CO, and CO_2) are not detected by a PID. Most instruments are typically outfitted with a 10.6 eV probe with the option of upgrading to an 11.7 eV probe, which is less robust under typical environmental conditions.

FIDs employ a hydrogen-fueled flame to ionize volatile compounds in air. Ionized molecules produce a current proportional to the total volatile organic vapor concentration in the air sample, which is then displayed by the instrument as a concentration on a meter or LCD display. FIDs can detect both smaller and larger aliphatic and aromatic hydrocarbons. Similar to PIDs, FIDs do not respond to ambient gases such as O_2, N_2, CO, and CO_2. Both FID and PID instruments are typically calibrated to one compound (methane and isobutylene are commonly used calibration compounds for FIDs and PIDs, respectively), and instrument response to other compounds or to a mixture is an integrated response.

There are several key differences between PID and FID instruments. PID instruments can respond to both organic and inorganic vapors, while FID instruments can typically respond to only organic vapors. Although both detectors can be sensitive to environmental conditions (e.g., extreme temperatures and humidity), PID detectors are normally more sensitive to environmental factors (in particular humidity) and are also sensitive to common voltage sources such as power lines, transformers, or other radio wave transmitters. In contrast to PID instruments, FID instruments can detect smaller chain aliphatics such as methane, for which there may be substantial background sources in or near people's homes (e.g., wetlands, sewers, septic fields, and decaying organic matter). PID instruments typically do not respond to methane because methane has an ionization potential of 12.98 eV that is higher than the ionization strength of the commonly used environmental probes. Depending on the lamp strength, PID instruments typically may respond weakly or not at all to gasoline-range aliphatics such as hexane and pentane, which have relatively high ionization potentials (10.18 and 10.35 eV, respectively). FID instruments also require the use, transportation, and storage of hydrogen gas, which is a flammable gas.

Photovac International, Inc. (now a division of Perkin-Elmer), HNu Systems, Inc., and Thermo Environmental are among the more recognized manufacturers of portable PID instruments, and popular models include the Photovac MicroTip, the HNu Model PI-101 Trace Gas Analyzer and the HW-101 Hazardous Waste Analyzer, and the Thermo Environmental OVM Logger Model 580B/S. The Foxboro OVA Models 108 and 128 and the Photovac MicroFID are popular FID instruments. Weekly rental costs are approximately $200-300 for most of these instruments.

PID/FID portable instruments are valuable instruments because they can provide real-time concentration data for vapors and gases in air. PID/FID instruments can be used to identify "hot spots," contaminant sources, and potential exposure pathways, thus assisting in site reconnaissance and rapid decision making towards a more refined sampling plan. However, these instruments should only be used as screening-level tools. As stated earlier, both PID and FID portable instruments respond to a wide variety of vapors and gases and yield a non-specific total vapor/gas concentration that should not be considered absolute or representative of actual contaminant levels. Concentration data are only semi-quantitative for a mixture of gases due to the use of only one calibration compound. These instruments also respond to many common interferences, such as humidity (both PID and FID instruments) and other voltage sources (PID instruments only), which can result in false positives and anomalous high concentration readings. In addition, these instruments are saddled by high detection limits (typically on the order of 0.2 to 1 ppm) and do not provide sufficient sensitivity to differentiate normal from problematic petroleum vapors.

Colorimetric Devices

Colorimetric devices are often used as a preliminary indicator of substance-specific vapor concentrations prior to FID, PID, or GC analysis. Substance-specific grab sample tubes or chips are available for specific compounds, including petroleum constituents such as benzene, toluene, ethylbenzene and xylenes (BTEX). Detection limits can be as low as 200 ppb for benzene but are typically on the order of 1 to 10 ppm for these compounds. Colorimetric tubes are also available for total petroleum hydrocarbons as a whole, but these tubes have high detection limits on the order of 10 ppm. Long duration detector tubes are available for the determination of time-averaged concentrations, but detection limits are typically higher for petroleum vapors (5 to 25 ppm).

For most colorimetric detection systems, a hand-held piston pump is used to pull a known volume of air through a tube at a predetermined flow rate. Personal sampling pumps are used for long-duration colorimetric detector tubes. During its passage through the tube, the contaminated air reacts with the detector reagents to produce a discoloration or stain. Most colorimetric tubes are graduated in ppm units and the length of the stain is proportional to the contaminant concentration. Sensidyne and Dräger are two commonly used brands of grab sample detector tubes. Pump kits typically cost between $300-400, and a set of 10 colorimetric tubes costs approximately $50.

National Dräger, Inc. has also recently developed a chip measurement system, which utilizes substance-specific chips and an automatic analyzer. The analyzer determines a measurement value according to the level of reaction between the air sample and the reagent material, and the result is displayed as a concentration in a digital readout. Only a limited number of chips are currently available, and these include a chip for benzene. The measurement range of the benzene chip is 0.2 to 10 ppm. The Dräger Analyzer Set costs approximately $1500; the benzene chip, which contains 10 measurements channels, costs approximately $130.

Several environmental and equipment factors limit the utility of colorimetric detection systems for indoor air assessment. Colorimetric tubes have traditionally been very sensitive to high moisture content and humidity, and temperature has also been demonstrated to influence the sensitivity and accuracy of detector tubes. Although improvements have been made in the new Dräger chip measurement system to reduce influences from humidity and temperature, the accuracy and sensitivity of substance-specific chips and tubes can also be impaired by interference with gases having similar chemical structures to the chemical of interest. Such interference is known as "cross-sensitivity" and is likely to occur for complex petroleum mixtures. Due to potential interferences, data from colorimetric detection systems should only be treated as "semi-quantitative."

Colorimetric detection systems may be useful as screening-level indicators of vapor concentrations where interfering compounds are restricting the use of other field measurement techniques. Colorimetric systems can provide immediate semi-quantitative concentration data and may be useful for confirming whether very high contaminant levels are present in indoor air and for indicating contaminant sources and pathways. However, due to high detection limits and possible interfering compounds, colorimetric tubes are likely of little use for quantitative indoor air assessment where a mixture of gases will be present and even sub-ppm levels of compounds can potentially be toxic, potentially the case for petroleum vapors.

Portable Gas Chromatography (GCs)

Portable GCs offer the advantage of real-time concentration data with compound separation, compound identification, and sensitive detection limits. Both short-term and long-term, time-integrated samples can be directly sampled and analyzed using a portable GC. Field GCs are more commonly used to analyze instantaneous (grab) samples, which can be injected via gas-tight syringes or pumped into the sample inlet port of the field GC. If equipped with sample loops and data loggers, field GCs can be used to collect continuous concentration data. In addition, field GCs can be used to obtain immediate results from grab or time-integrated samples collected using such sampling containers as SUMMA® canisters or Tedlar sampling bags (see below discussions on these sampling

methods). Sensitive detection limits (on the order of 1 ppb) can be obtained for sample analytes such as benzene, toluene, ethylbenzene, and xylenes.

Gas chromatography utilizes a sample injection system for sample introduction, a chromatographic column for compound separation, and one or more detectors for identification and quantification of individual compounds. Samples can be introduced into a GC via a syringe or pump, or GCs can be fitted with integrated or add-on gas sampling valves for direct air sampling. Chromatographic columns typically consist of absorbent materials and separate compounds based on their boiling points and their affinity for the column. Both packed and capillary columns are now available for portable GCs. A carrier gas (typically helium) and temperature are used to move compounds down the column. Most portable GCs are isothermal, which differs laboratory GCs which can be temperature-programmed. Most compounds exit the column and enter the detector (normally a PID or FID for petroleum hydrocarbons; see above text for descriptions of PID/FID detection systems) at different, but reproducible, rates. Detector responses are recorded for these different retention times on either a strip chart recorder or an automated data acquisition system. Compounds can be identified according to their retention times and quantified according to the response of known calibration standards.

Popular portable GCs include the Photovac SnapShot, 10S 50, and 10S Plus Portable Gas Chromatograph and the HNu Models 311 and 321 Field Transportable GCs. All of these GCs are typically outfitted with a PID detector with the option of installing a FID. While most portable GCs require some set-up space, the SnapShot has the unique capability of being hand-held. Detection limits for VOCs such as benzene, toluene, and xylenes in preconcentration samples can be as low as 1 to 10 ppb for these instruments, potentially even lower for those which have pre-concentrator capabilities.

Weekly rental prices for commonly available portable GCs are approximately $1000-1500. These costs do not include the cost of calibration materials and sampling media (which may include Tedlar sampling bags). Used portable GCs can be purchased for approximately $10,000-15,000, while new portable GCs list for approximately $20,000-30,000. Training on portable GC use and maintenance are available from manufacturers, including Photovac.

Equipment and environmental conditions can impair the field performance of portable GCs. Extreme temperature and high humidity can cause potential problems, and instruments should be field-calibrated before each use to diagnose and correct for these potential problems. Temperature fluctuations can lead to erratic retention times and interfere with compound identification. For complex mixtures such as petroleum vapors, interference by co-eluting compounds can reduce instrument sensitivity and accuracy. Inefficient compound separation can result in high levels of some compounds swamping the signal of other low-level contaminants; this can be a particular problem for a PID detector because the PID has varying sensitivities for different compounds. In addition, portable GCs are typically not simple instruments, and the user must be skilled at operating

the instrument as well as interpreting data. Field GCs can be difficult to optimize for sensitivity and accuracy when the goals are to detect compounds with very different boiling points or several compounds present at both high and low concentrations. Without preliminary compound identification through the use of calibration standards or chromatogram fingerprinting, it can be very difficult to identify "unknown" compounds using a portable GC. Calibration with the proper standards is essential for the positive identification and quantification of target analytes. In addition, proper maintenance is essential to the long-term sensitivity and accuracy of an instrument, in particular for GCs which are frequently exposed to both high and low concentration levels. Instrument parts and columns can become coated with contaminants, thus reducing sensitivity and making it very difficult to obtain accurate readings for low-level samples. A strict maintenance and calibration schedule is necessary to ensure the long-life of the instrument.

Portable GCs are very useful for both short-term and long-term monitoring of indoor air due to their versatility and sensitivity. Portable GCs can be used to collect and analyze grab samples and, if equipped with sample loops and data loggers, field GCs can be used to collect continuous data. Continuous sampling can identify peak exposures as well as provide longer term exposure data. Detection limits are likely to be elevated for continuous sampling because there would be no sample pre-concentration. As mentioned above, data quality and usability are highly dependent upon the operator's capabilities as well as instrument maintenance and calibration.

Methods Requiring Laboratory Analysis

Organic Polymeric Absorbents (e.g., EPA Method TO-1)

Organic polymeric absorbents have seen widespread use for the collection of time-integrated samples. Polymeric absorbents and other solid absorbents have also been used in passive samplers such as sampler badges, which rely on simple diffusion of volatiles into the badge during long exposure periods (e.g., 30 days). Among the most widely used commercial organic polymer absorbents are Tenax™, XAD (styrene-divinylbenzene copolymer) resins, and Ambersorb™. Tenax GC™ (poly(2,6-diphenyl phenylene oxide) is used in EPA Method TO-1 and was chosen as the absorbent by U.S. EPA for the Total Exposure Assessment Method (TEAM) Studies, which investigated personal exposures of about 800 persons in selected urban and rural communities to many VOC compounds. Tenax™ is a thermally stable and hydrophobic sorbent, and these properties have resulted in its widespread use for sample collection of C5-C6 to $\geq$ C18 hydrocarbons.

Sampling methods employing polymeric absorbents consist of two processes: the capture process and the compound recovery process. Polymeric absorbents are typically used as a component of active samplers, where air is drawn through a sample cartridge by a calibrated pump. As the air passes through the sample cartridge containing the polymeric absorbent, nonpolar VOCs are retained by the hydrophobic medium.

The capture process is followed by the compound recovery process, and thermal desorption is most often used to release VOCs from organic polymeric absorbents for laboratory analysis. Thermal desorption is most useful for compounds with boiling points less than 300^{o}C. Among the reasons why Tenax™ is so widely used is that it is of high thermal stability, which facilitates the efficient, clean recovery of collected VOCs via thermal desorption.

Polymeric absorbents can be used to sample large quantities of air, thus allowing for low detection limits for individual compounds (typically <1 ppb). Due to the capability to sample large volumes of air, organic absorbents are often used to collect time-integrated samples. Polymeric absorbents are also very portable and easy to install. Costs per sample are generally $20-50 for sample cartridges/tubes, approximately $70 for rental of a personal sampling pump, and $175 for laboratory analysis (typically by GC-MS as required in EPA Method TO-1, or by GC-PID and/or GC-FID).

Sorbent sampling is also subject to several problems, several of which are particularly exacerbated for petroleum vapors such as benzene. Key sorbent criteria include breakthrough volume, required sample volume, blank value of clean sorbent, desorption efficiency, and sorbent thermostability. Sample breakthrough is a problem for all methods employing solid absorbents, particularly when time-integrated samples are collected. Sample breakthrough occurs when compounds are not retained by the collection medium during sampling. The potential for breakthrough is a function of several variables including sample volume, pumping rate, vapor concentrations, temperature, sorbent type, and the size of the sorbent trap. Backup traps are often installed in series behind the primary trap to determine if sample breakthrough may be occurring. Numerous studies have examined sample breakthrough volumes for various compounds, and these studies have demonstrated that the precision of the method is relatively poor for several compounds including benzene (Yocum and McCarthy, 1991).

Background contamination of sorbent material is also a potential problem for this method. Sorbent cartridges are typically cleaned via thermal desorption or solvent extraction, but analyses of unused Tenax™ cartridges have demonstrated that many compounds, including benzene, ethylbenzene, and xylenes, are still present at detectable levels in cleaned cartridges (Hines, 1993). Quality control/quality assurance (QA/QC) studies have also shown that recoveries of some compounds are often greater than 100% for thermal desorption of Tenax™, indicating that either the sorbent material is acting as a catalyst and converting some compounds to other compounds or that the sorbent material itself is breaking down during thermal desorption. Artifact formation can thus interfere with thermal desorption analyses, and such interference can be very problematic because thermal desorption analyses use the entire sample and thus allow for only one sample run. These studies indicate that the proper cleaning and storage of the sorbent material is essential to obtaining reproducible and accurate results.

Although polymeric organic sorbents such as Tenax™ have seen widespread use for the collection of time-integrated air samples, there are problems associated with these methods, in particular for complex mixtures such as petroleum hydrocarbons. Breakthrough can potentially occur if contaminant levels are high and large sample volumes are collected, and background contamination and artifact formation can also lead to false positives and anomalously high results. In addition, only one sample run is possible for thermal desorption samples. Special care should be taken to prevent these problems from occurring if Tenax™ is to be used to collect time-integrated indoor air samples in residences where there is petroleum contamination.

Carbon Molecular Sieves (e.g., EPA Method TO-2)

Carbon molecular sieves are used for sample collection in EPA Method TO-2. Spherocarb and Ambersorb XE-340 are examples of commercially available graphitized molecular sieves. These solid absorbents are very similar to Tenax™ absorbents, and much of the above discussion for polymeric organic absorbents also holds for carbon molecular sieves. The major difference between carbon molecular sieves and Tenax™ absorbents is that compound extraction can be less efficient for this medium, especially for very volatile compounds. Extremely high desorption temperatures are necessary to efficiently remove compounds, and these temperatures decrease the recovery of high boiling point compounds and increase the likelihood of thermal decomposition problems and artifact formation. Low sample recoveries and interferences can thus be associated with air sampling involving carbon molecular sieves.

Activated Carbon (e.g., ASTM Method D 3686-84)

Activated carbon is a solid absorbent that has traditionally been used to monitor the workplace environment. Small sample volumes have been typical for the monitoring of the workplace environment due to high contaminant levels, and sample breakthrough is a potential problem with activated carbon for monitoring of low-level environments where larger sample volumes are necessary for analyte detection. Activated carbon has been used for low-level indoor air assessment, but it is being rapidly replaced by polymeric carbon absorbents as the absorbent of choice (Hines, 1993). Activated carbon has the disadvantage of requiring the use of organic solvents for compound removal, and solvents are not normally the extraction method of choice for volatile organic compounds because solvents can be a source of background contamination and the solvent extraction process results in sample dilution and decreased sensitivity. In addition, activated charcoal has a greater affinity for water than organic polymeric absorbents, and retention of water in moist environments can prevent sample analysis.

SUMMA® Stainless Steel Canisters (e.g., EPA Method TO-14)

Pre-evacuated SUMMA® passivated stainless steel canisters are recommended in EPA Method TO-14 for the collection of whole air samples. The SUMMA® passivation

process refers to the treatment of the interior of the canisters to produce a surface of pure chrome nickel oxide. This special electropolish coating is intended to prevent sample decomposition. Pre-evacuated SUMMA® stainless steel canisters are frequently used to collect time-integrated indoor air samples, but they can also be used to collect grab samples.

In contrast to solid absorbents, the collection and analysis of air samples using stainless steel canisters only involves two simple steps: the collection of air in the canister and the direct analysis of the sample. Samples are typically collected under either pressurized or subatmospheric pressures. In both cases, a pre-evacuated canister is used with a sampling train that typically includes a particle filter, a flow restricting device (e.g., a mass flow controller or a critical orifice flow restrictor), and a Magnelatch valve. The only major difference between sampling equipment for pressurized or subatmospheric sample collection is the use of a sampling pump to introduce sample under pressurized conditions. The most common sample volume for SUMMA® canisters is 6-L, and this sampling volume is typically used to collect both 8-hour and 24-hour time-integrated samples. Weekly rental of pre-evacuated SUMMA® passivated stainless steel canisters costs approximately $50, and pre-calibrated flow controllers rent for approximately $20/week.

One of the key advantages of SUMMA® canisters is that the sample volume is not limited by the breakthrough capacity as it is for solid sorbents. This capability of SUMMA® canisters is especially useful for sampling in areas of unknown contamination or when contaminant levels may vary. In addition, QA/QC studies have demonstrated that blank contamination is typically less of a problem for SUMMA® canisters than for solid absorbents. Furthermore, only a portion of the air collected in a SUMMA® canister is used for sample analysis, thus permitting more than one sample run if necessary. Condensation of large amounts of moisture was formerly a potential problem with SUMMA® canisters, but a drying step is normally incorporated into sample preparation so that moisture is removed before it can corrupt sample analysis.

The bulky, sophisticated nature of pre-evacuated SUMMA® passivated stainless steel canisters formerly limited their widespread use for indoor air assessment. However, canister set-up has been greatly simplified, and SUMMA® canisters are now very portable and easy to operate.

Tedlar Sampling Bags

Similar to SUMMA® stainless steel canisters, Tedlar sampling bags are an air displacement container. The bag is evacuated prior to use and air is collected by opening an inlet and using a pump for positive pressure. Tedlar sampling bags are more commonly used to collect grab samples although they can also be used to collect time-integrated air samples. Tedlar bags are not as widely used as SUMMA® canisters for the collection of

longer term time-integrated samples, in part because there can be contact between and loss of compounds to the bag material.

Depending on the bag size, Tedlar bags cost approximately $10 each. Adapters and fittings must also be purchased.

LABORATORY ANALYTICAL METHODS

The goals of analytical protocols are typically to separate, identify and quantify VOCs collected in an air sample. As discussed earlier, portable PID/FID instruments can be used in the field to provide immediate, semi-quantitative information on total organic vapor concentrations. Direct-reading colorimetric systems and tubes may be useful as field screening tools, but these methods are subject to higher detection limits and potential interferences, particularly for complex mixtures such as petroleum vapors. Portable GCs can also provide real-time concentration data, particularly for grab samples; however, deployment of GCs in the field may not be a practical option due to cost, technical feasibility, and extreme environmental conditions.

To obtain adequate sensitivity and accuracy, it is often necessary to separate the sampling and analytical components of indoor air analysis. Laboratory gas chromatography (GC) or gas chromatography/mass spectrometry (GC/MS) are often necessary analytical techniques for positive identification and precise quantification of trace levels of volatile contaminants in air samples.

As discussed above, Table E-1 summarizes information on analytical as well as sampling methods commonly used for petroleum vapors. Methods that require laboratory analyses are separated from field screening methods. Most of the information presented on analytical methods in the table and text is based upon discussions with and price quotes prepared by two full-service air quality laboratories (Air Toxics, Ltd., Folsom California; and Performance Analytical, Inc., Canoga Park, California). The following discussion of analytical methods begins with a brief description of two commercially available GC analytical methods, Boiling Point Distribution Range Analysis and Analysis of Ozone Precursors. GC-MS analysis is then briefly described

Evaluation of Analytical Methods

Boiling Point Distribution Analysis

Boiling Point Distribution Analysis is an analytical method offered by Air Toxics, LTD This method utilizes a GC equipped with a PID and FID in series to identify and quantify both petroleum constituents and hydrocarbon ranges. Aromatic volatile organics (e.g., BTEX) are quantified using the PID detector, and hydrocarbon ranges are quantified using

the FID detector. Detection limits for the individual aromatic compounds are 1 ppbv, while detection limits for total petroleum hydrocarbons is 10 ppbv. Sample carbon ranges include: C_2-C_5 hydrocarbons, C_5-C_6 hydrocarbons, C_6-C_7 hydrocarbons, . . ., C_{12+} hydrocarbons. Air Toxics typically uses gasoline and jet fuel as calibration standards for the boiling point ranges.

Air Toxics charges $150 per analysis for this service.

Analysis of Ozone Precursors

Analysis of Ozone Precursors is an analytical method offered by Performance Analytical, Inc. This method utilizes a GC-FID to identify and quantify 75 alkanes, alkenes, and volatile aromatic hydrocarbons. Detection limits are 1 ug/m^3 (< 1 ppbv) for each compound.

Performance Analytical charges $150 per analysis for this service. For an additional $25 per sample, Performance Analytical will report concentration data for three volatile petroleum hydrocarbon fractions to evaluate human health risk at petroleum-contaminated sites: C_5 to C_8 alkanes and cycloalkanes, C_9 to C_{12} alkanes and cycloalkanes, and C_9 to C_{12} aromatics and alkenes.

Gas Chromatography with Mass Spectrometry (GC/MS)

Analysis by GC/MS is required in EPA Methods TO-1, TO-2, and TO-14. Although more expensive and sometimes less sensitive than laboratory GC-PID/FID analyses, U.S. EPA recommends GC/MS analysis because mass spectrometers are capable of both positive identification and primary quantification (U.S. EPA, 1992). GC/MS systems are less subject to common analytical problems such as variable specificity and sensitivity, non-positive compound identifications, and lack of resolution of co-eluting compounds. GC/MS relies on both compound retention time and compound fragment pattern for positive compound identification. GC-MS systems offer positive identification for both known target analytes and unknown analytes because they can be run in two different modes. The selected ion monitoring mode is typically used to identify and quantify a set list of compounds because slightly lower detection limits are possible in this mode. The scan mode is used to identify and quantify any and all compounds in a sample.

Both Air Toxics and Performance Analytical offer GC-MS analyses to support EPA Methods TO-1, TO-2, and TO-14. Each laboratory has validated a list of compounds that they identify and quantify in a full scan. Air Toxics has a validated list of 61 compounds, and their GC/MS Full Scan costs approximately $250. Performance Analytical has a validated list of 43 compounds, and their GC/MS Full Scan costs approximately $225. Detection limits for both laboratories are typically less than 0.5 ppbv for each compound.

These validated lists include many compounds which are not petroleum-related (i.e., chlorinated solvents, Freons, etc.), and cost savings are available from both laboratories for abbreviated compound lists. For example, Performance Analytical charges approximately $110 for analysis of one compound on their validated list with additional costs of $10 per compound up to a total of 10 compounds. Air Toxics charges approximately $175 for analysis of 1 to 5 compounds.

Both labs will identify and quantify compounds not on their validated lists as tentatively identified compounds (TICs) for additional cost. Performance Analytical charges $70 for up to 15 TICs, and Air Toxics charges $50 for 10 TICs. The identification of compounds not on the validated lists is essential for the quantification of volatile petroleum fractions. In previous analytical reports prepared for indoor sampling of Maine residences, Air Toxics has reported data for total petroleum hydrocarbon (TPH) fractions such as C_2 to C_7 hydrocarbons, C_{8+} hydrocarbons, etc. Both laboratories stated that it is possible to quantify petroleum fractions using GC/MS, but Performance Analytical suggested the Ozone Precursor Analysis as a more appropriate alternative analytical method.

APPENDIX F - Human Health Effects Associated with Petroleum Product Vapors

HUMAN HEALTH EFFECTS ASSOCIATED WITH PETROLEUM PRODUCT VAPORS

The toxicity of petroleum products varies due to the hydrocarbon compounds that make up each product. This section summarizes toxicity information available for gasoline, kerosene, fuel oil and several important petroleum constituents. Petroleum hydrocarbons are comprised of compounds that have varying degrees of toxicity. For toxicological purposes, they can be divided into two very broad classes: the alkane/cycloalkane compounds (aliphatic fraction) and the aromatic/alkene compounds (aromatic fraction)..

Most toxicity information available for the aliphatic fraction of petroleum hydrocarbons is for the alkanes. Such studies focus on short-term exposures that cause mucous membrane irritation or disruption of the central nervous system (CNS). CNS effects are commonly associated with exposure to the lower molecular weight compounds (C_5 to C_8 carbon range). Animal studies indicate that narcotic activity within the C_5-C_8 compounds range increases as a function of carbon chain length, but narcotic activity decreases in potency beyond C_9 compounds (MADEP, 1994).

The aromatic fraction of petroleum hydrocarbons can generally be divided into benzene, its derivatives (toluene, ethylbenzene, and xylene), and polycyclic aromatic hydrocarbons (PAHs). Alkyl benzenes are generally CNS depressants due to their affinity for nerve tissue and may also produce kidney and liver effects (MADEP, 1994). Common effects associated with PAHs include dermal irritation, blood toxicities, and kidney and liver effects.

Gasoline

Acute inhalation exposures to 500 ppm gasoline result in central nervous system effects such as drowsiness, headache, dizziness and nausea. At concentrations of 1,000-5,000 ppm, convulsions and deliriums, are possible while at concentrations greater than 5,000 ppm, coma and death may occur (ATSDR, 1993).

There is one study performed in rats that evaluated developmental endpoints, but the results were inconclusive (reviewed in Skalko, 1993).

Unleaded gasoline is associated with male rat kidney tumors; however, it is now widely accepted that these types of tumors are not predictive of carcinogenicity in humans and should not be considered in the weight-of-evidence assessment. There is evidence that gasoline is carcinogenic based on the increased incidence of hepatocellular adenomas/carcinomas in female mice (USEPA, 1987).

Kerosene

Very few data are available on the health effects of kerosene. Most of the studies in which humans have been exposed to kerosene via inhalation are uncontrolled for inhalation of other substances, and there is no information on the concentrations or doses to which subjects were exposed. Exposure to relatively high concentrations of kerosene can result in headaches, poor coordination, and other neurological effects (ATSDR, 1993). Limited epidemiological data suggest that long-term inhalation exposures to kerosene vapors and/or kerosene combustion products from cooking with kerosene stoves does not induce

asthmatic respiratory effects (ATSDR, 1993). There are no data available to evaluate the potential for carcinogenicity of kerosene.

Fuel Oils

The toxicity of fuel oils (including diesel fuel and home heating oil) is based on data from exposures to jet fuel vapors. Acute inhalation of vapors can result in dizziness, headache, difficulty concentrating, and nausea. Chronic inhalation may result in fatigue, mood changes, and anxiety. Data from animal studies suggest that fuel oils are not reproductive or developmental toxins, although the data are limited and some of the studies are questionable (Lock et al., 1984; Beliles and Mecler, 1983).

Benzene

Acute exposure to benzene may result in nausea, vomiting, ataxia and excitement. Benzene depresses central nervous system function. Narcotic effects, similar to those produced by toluene "glue sniffing," may occur. Chronic exposure to benzene is known to cause adverse hematological effects (ATSDR, 1989) such as a reduction in the number of red blood cells, white blood cells, and platelets in addition to central nervous system effects.

Several epidemiological studies have associated occupational benzene exposure with an increased incidence of leukemia (USEPA, 1984). As a result, EPA classifies benzene as a known human carcinogen. Until recently, studies in animals did not conclusively support the evidence that benzene is a human leukemogen. For instance, IARC (1982) concluded that there is only limited evidence that benzene is carcinogenic in experimental animals. However, a recent study (NTP, 1984) found that "under the conditions of these studies, there was clear evidence of carcinogenicity of benzene" for F344/N rats and B6C3F1 mice of both sexes.

Evidence from human and animal studies suggest that benzene may be a reproductive and developmental toxin, although the studies from which these conclusions are drawn were not well designed (ATSDR, 1995).

Ethylbenzene

Humans exposed to moderate levels of ethylbenzene in air for short periods of time may experience eye and throat irritation. Exposure to higher levels may cause more severe effects such as central nervous system depression, decreased movement and dizziness, mucous membrane irritation, and respiratory depression. One study in which rats were exposed to ethylbenzene vapors demonstrated fetotoxicity at concentrations that produced maternal toxicity (Andrew et al., 1981).

There is some evidence that ethylbenzene possesses some potential for mutagenesis, although its carcinogenicity in a chronic oral bioassay was inconclusive (NTP,1990).

n-Hexane

Inhalation of n-hexane may result in irritation of the mucous membranes and respiratory tract. Acute exposure may cause nausea, headache and dizziness. At high concentrations, asphyxia may occur (Sittig, 1985). Long-term human exposure to n-hexane vapors has been shown to cause peripheral neuropathies in addition to blurred vision, cranial neuropathy and abnormal color vision (Cassarett & Doull, 1996). The onset of symptoms may be delayed for several months to a year after the beginning of the exposure. Some individuals recover completely, but others are left with permanent nerve damage. Animal models have been used to document the pathology of these effects. In addition to peripheral neuropathies in mice, there were mild lesions of the nasal turbinates (Dunnick et al., 1989). n-Hexane has been shown to cause testicular atrophy in rats exposed to 1000 ppm n-hexane. There is no evidence that n-hexane causes cancer in humans.

Methyl* tert-*butyl ether (MTBE)

Many of the harmful effects seen following exposure to gasoline are due to the individual chemicals in the gasoline mixture. One of these chemicals is methyl *tert*-butyl ether (MTBE). MTBE is sometimes added to gasoline to increase oxygenation and make it burn more cleanly. Some people who were exposed to high levels of MTBE while pumping gas or working at a gas station subsequently complained of headaches, nausea, dizziness, confusion, and irritation of the nose or throat (Johanson et al, 1995).

More is known about MTBE's animal health effects than human health effects. The most common effect of inhalation of MTBE in animals is action on the nervous system. Rats and mice intermittently exposed to a minimum of 3,000 ppm MTBE in air during chronic duration studies showed signs of neurotoxicity, including hypoactivity, staggering and falling. These effects were short-term and after about an hour, the animals seemed normal again. Animals that breathed MTBE exhibited irritation of the nose and throat.

Rats exposed intermittently for four to five weeks to 3,000 ppm MTBE showed increased liver weights as did mice that breathed MTBE at a minimum concentration of 3,000 ppm for 18 months. Breathing MTBE for a year and a half at a concentration of 8,000 ppm resulted in an increase in liver tumors in mice (Savolainen et al, 1985). Female rats exhibited increased kidney weights after exposure to a minimum concentration 3,000 ppm MTBE in air for up to 24 months. In both male and female rats, age-related kidney disorders were exacerbated by inhalation of MTBE.
Exposure of female mice to 8,000 ppm MTBE resulted in developmental effects including reduction in fetal body weight and number of viable implantations as well as an increase in fetal malformations. There is no indication that MTBE has any reproductive effects.

MTBE has not yet been classified for its ability to cause cancer in humans. It is not known whether MTBE can cause birth defects in humans (ATSDR, 1996).

Naphthalene

In humans, exposure to sufficient concentrations of naphthalene through inhalation, ingestion, or dermal contact may cause intravascular hemolysis or the less severe symptoms of eye irritation, headache, confusion, tremors, nausea, vomiting, abdominal pain and bladder irritation (Sittig, 1985). In severe cases hematological effects have included red cell fragmentation, icterus, severe anemia, leukocytosis and dramatic decreases in hemoglobin, hematocrit and red cell counts. Hemolysis can also lead to renal disease from precipitated hemoglobin (USEPA, 1982). Poisonings have occurred in humans as a result of the ingestion of mothballs as well as from clothing infants in materials that have been stored in mothballs.

The National Toxicology Program (NTP, 1992) recently found limited evidence for the carcinogenicity of naphthalene. In this study, mice were exposed to naphthalene via inhalation for two years.

There are limited data on the toxicity of the methylnaphthalenes. However, based on their structural similarity, it is likely that they will behave similarly to naphthalene.

n-Nonane

n-nonane is a constituent in the paraffin fraction of crude oil and natural gas. This compound is highly volatile; therefore, the most probable route of human exposure is by inhalation. There is no available human toxicity information for n-nonane, and very little data from animal systems. Human inhalation of n-nonane is reported to be irritating to the eyes and the respiratory tract. Exposure to n-nonane vapors may result in dizziness or suffocation (U.S. DOT North American Emergency Response Guidebook 1996). Adipose, liver and brain tissues seem to have the highest affinity for n-nonane. The toxicity of n-nonane is believed to result in neurotoxic effects of lesser magnitude than those caused by shorter chain alkanes. Rats exposed for six hours a day for seven days to 1,500 ppm n-nonane showed increased salivation, slight coordination loss, irritation of eyes and mild tremors. Rats exposed to 1,600 ppm n-nonane for six hours a day, five days a week, for thirteen weeks had significantly lower mean body weight gains than the controls. Two deaths occurred. No effects were observed at 590 ppm (Carpenter et al., 1975).

There is no information available on the teratogenicity or carcinogenicity of n-nonane.

Toluene

In humans, acute exposure to high levels of toluene vapors may cause central nervous system (CNS) depression. Acute exposures may result in reversible depression of the CNS,

neurological dysfunction, impaired performance and narcosis. Chronic exposure to moderate to high concentrations of toluene is associated with CNS disturbances and impaired neuromuscular function. At high levels of exposure, ataxia, tremors, speech, hearing and vision impairment have been reported in longtime abusers of toluene (ATSDR, 1989). Toluene vapors are irritating to the respiratory tract.

Chronic exposure has been reported to result in permanent CNS effects such as ataxia, tremors and impaired speech, hearing and vision. Inhalation of 200-300 ppm for 1-10 years may cause loss of coordination, impaired memory and thinking ability. Liver, kidney, cardiovascular, immunological and respiratory disturbances have been noted at high doses or prolonged exposures (ATSDR, 1989).

Animal exposures to moderate to high concentrations of toluene have produced developmental effects including skeletal abnormalities and decreased fetal weight (Ungvary, 1985) in addition to CNS and hepatic effects.

Toluene has been tested for carcinogenicity in a number of dermal and inhalation studies using experimental animals. There is no evidence that toluene is carcinogenic.

Xylene

When inhaled, xylene(s) cause CNS effects that may include irritation of the respiratory tract, headaches, dizziness, nausea, tremors, unconsciousness and coma depending on the dose and duration of exposure. There is some evidence suggesting that xylene(s) can precipitate heart failure and death (ATSDR, 1993) as demonstrated in animal systems. Animal studies also suggest that xylene(s) may result in kidney damage and developmental effects (Marks et al., 1982; Ungvary et al., 1980).

No studies indicate that xylene is carcinogenic or mutagenic.

APPENDIX G - Derivation of Human Health-Based Action Levels

DERIVATION OF INDOOR AIR ACTION LEVELS

This appendix describes three Action Levels for each petroleum indicator compound. The rationale for the selection of the indicator compounds is in Appendix C. Action Levels represent concentrations in residential indoor air that when exceeded in the living space, require additional sampling, corrective action, and/or evacuation. The action levels are either toxicity-based concentrations or background concentrations. The higher of the two values is the Action Level. The Action Levels are all toxicity-based with the exception of the chronic Action Level for benzene because benzene's average background concentration is higher than the toxicity-based chronic concentration. The background benzene concentration was identified after reviewing available residential indoor air benzene concentration data described in Appendix I. The Action Levels are presented in Table G-1.

The Action Levels are intended to protect sensitive individuals from significant health effects associated with inhalation exposures to compounds found in gasoline, kerosene, and home heating oil. Sensitive individuals include pregnant women, young children, elderly people, individuals with compromised immune systems, and individuals in the general population who may be susceptible to the toxic effects of a chemical due to their genetic make-up. We used data from human toxicity studies (where available) and animal studies to derive the Action Levels. For some compounds such as benzene and toluene, there are substantial amounts of quality data from which to derive an Action Level. For other compounds such as n-nonane, hexane, and naphthalene, there are significantly less data from which to derive Action Levels. Confidence in the Action Level is proportional to the amount and quality of available data. As additional toxicity data are generated for indicator compounds, Action Levels must be re-evaluated. The Action Levels can be refined, if necessary, by using pharmacokinetic parameters specific to the animal model in which the critical effect and dose was identified. These changes will likely result in an increase in the Action Level. We anticipate that during the Trial Period, it will be determined whether such refinement is necessary.

Three Action Levels are set for each petroleum indicator compound. These Action Levels represent protective indoor air concentrations for acute (1-14 days), subchronic (15 - 364 days), and chronic (365 days or more) exposure durations.

Toxicological data sets are robust for benzene, ethylbenzene, toluene, and xylenes. There are significantly less data on which to base a guideline for n-hexane, n-nonane, and naphthalenes. At present, there are insufficient data from which to derive acute Action Levels for n-hexane and n-nonane. The subchronic and chronic guidelines for n-nonane are particularly uncertain. It is recommended that these values be used judiciously until the data set is supplemented with additional information. All of the Action Levels should be revisited as the data set on which they are based expands.

Table G-1

Summary of Action Level Derivation Method

To develop Action Levels, we used general methods used by the USEPA, the National Research Council (NRC), and the Agency for Toxic Disease Registry (ATSDR). All of these organizations rely on health effects data generated for humans or animals, identification of critical endpoints and associated effect levels, and application of uncertainty factors where needed to protect the desired individuals in the population. We reviewed and adopted technically defensible, toxicity-based indoor air concentrations derived by these organizations for some indicator compounds (Table G-1).

USEPA derivies inhalation reference concentration values (RfCs). An RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime. The RfCs are protective of sensitive sub-populations in a residential situation.

ATSDR derives health-protective levels for acute, subchronic, and chronic durations called Minimal Risk Levels (MRLs). Like the RfC, inhalation exposure levels are adjusted for continuous exposures (i.e., 24 hours/day, 7 days/week). Uncertainty factors are used to protect sensitive subpopulations and to account for interspecies variability.

The NRC Toxicology Subcommittee has derived Spacecraft Maximum Allowable Concentrations (SMACs) for selected airborne contaminants (NRC, 1994; NRC, 1996). The SMACs are health-protective levels of contaminants that might be encountered in the space-station environment. They have been derived for 1 hour, 24 hour, 7 day, 30 day, and 180 day exposures. We have reviewed the SMACs developed for benzene, ethylbenzene, toluene, and xylene. Since these values are not health protective for a residential situation, we do not recommend them.

In instances where both a USEPA-derived RfC and an ATSDR-derived MRL are available, we adopted the RfC as the Action Level. When only an MRL is available, we reviewed the choice of key study and the derivation. If technically defensible, the MRL was adopted for use as an Action Level. For compounds with no USEPA or ATSDR-derived health protective levels, the RfC methodology was applied to existing toxicological data.

The chronic Action Levels are equivalent to the RfCs developed by the USEPA. RfCs pertain to continuous exposures for a lifetime. However, if exposure assumptions are changed and appropriate toxicological data utilized, Action Levels may be calculated for exposure durations of less than a lifetime (i.e.. acute and subchronic Action Levels).

US EPA Approach to Deriving RfCs

RfCs are derived as follows:

$$RfC_{[HEC]} = NOAEL_{[HEC]} / (UF \times MF)$$

where:

$NOAEL_{[HEC]}$ = no observed adverse effect level (NOAEL), adjusted for dosimetric differences between animal species and humans, expressed as human equivalent concentration as follows:

$NOAEL_{[HEC]}$ (mg/m^3) = $NOAEL_{[ADJ]}$(mg/m^3) x $[(V_A/BW)_A]/[(V_A/BW)_H]$

$[(V_A/BW)_A]/[(V_A/BW)_H]$ = the ratio of the blood:gas(air) partition coefficient of the chemical for the experimental animal species to the human blood:gas(air) partition coefficient (for extra respiratory effects).

UF = an uncertainty factor suited to the characteristics of the data, and

MF = a modifying factor based on professional judgment of the entire data base (e.g., sample size of chosen study).

Many inhalation toxicity studies entail exposure regimens that are discontinuous. Often exposures are for 6-8 hours/day and 5 days/week. A normalization to 24 hours/day for a lifetime of 70 years is needed to adjust for the wide variety of experimental exposures to permit comparisons between studies. The RfC is intended to reflect lifetime continuous exposure; therefore it must be normalized to account for this exposure duration. To calculate duration-adjusted exposure levels in mg/m^3 for experimental animals, the appropriate equation is:

$NOAEL_{[ADJ]}$(mg/m^3) = E(mg/m^3) x D(hours/24 hours) x W(days/7days)

where:

E = experimental exposure level,
D = number of (hours exposed/day)/24 hours, and
W = number of (days of exposure/week)/7 days.

The three Action Levels rely on the identification of the NOAEL for the critical effect from published literature. If the NOAEL is taken from a study in which the exposure is not continuous, then the NOAEL is adjusted for continuous exposures ($NOAEL_{[ADJ]}$). The $NOAEL_{[ADJ]}$ is converted to the $NOAEL_{[HEC]}$ by accounting for the differences in dosimetry between animals and humans. Pharmacokinetic parameters specific to the vapor and animal test species are used in this calculation. In the absence of chemical/test animal specific information, a default value of “1” is used.

Time adjustment for discontinous exposures is the default approach in the absence of information about whether adverse effects are time or concentration dependent. When there is information indicating that a chemical's effects are exposure concentration-dependent and not duration dependent, then adjustment for intermittent exposure is obviated. Exposure concentration-dependent means that the biological elimination mechanisms are not saturated, and the chemical is rapidly eliminated from the body of the test species. Chemical exposures likely to be time-dependent are ones involving lipophilic compounds that tend to accumulate in tissues. Following inhalation exposure, xylenes are rapidly absorbed and eliminated and toluene blood level quickly reaches a plateau. Consequently, adverse effects associated with these compounds are concentration-dependent, and there is no need to perform the time adjustment. For this reason, ATSDR stands behind its acute MRLs for these two compounds that are not adjusted for time. In contrast, benzene action levels are adjusted for time because benzene is lipophilic and accumulates in tissues.

The uncertainty in the Action Levels is, in part, reflected in the magnitude of the factors applied to the concentration associated with the critical effect. As stated previously, the more confidence in the data set, the less uncertainty in the Action Levels and the lower the magnitude of the uncertainty factors. We have applied the USEPA uncertainty factors in the derivation of these Action Levels.

The Action Levels for the indicator compounds have been compared with available toxicity data for whole petroleum products. The whole product toxicity data are presented in Tables G-2 and G-3. This “reality check” allowed us to determine whether there were toxicity endpoints identified for the whole product that were not identified for any individual indicator. This was not the case. Our comparison also allowed us to determine whether any of the Action Levels for the indicator compounds were higher than those effect levels reported for the whole products. Not surprising, all of the Action Levels for the indicator compounds were below the effect levels for the whole products.

Presented below are the toxicity summaries and the basis for each Action Level for the indicator compounds.

Benzene

Toxicity Summary

Inhalation of high concentrations of benzene (300 to 3,000 ppm), can result in headache, dizziness, drowsiness, delerium, tremor, and loss of consciousness. Exposures to higher concentrations can result in death due to asphyxiation, respiratory arrest, central nervous system depression or cardiac arrest (ATSDR, 1996).

During longer exposures that are below the CNS threshold, it appears that metabolites of benzene may be responsible for inducing toxicity that is mediated through damage to stem

cells in the bone marrow (NRC, 1996). Exposures to benzene vapors for several months to several years has been shown to reduce the number of blood cells (erythrocytes, leukocytes, and thrombocytes) in animal and human studies. Exposures to C57BL/6 mice of 10 ppm benzene for 6 days resulted in a reduced capacity of the bone marrow cells to produce mature B-cells (Rozen et al., 1984). When treated for 6 and 23 weeks at 300 ppm, there was a decrease in the numbers of B- and T-cells (Rozen and Snyder, 1985). Continued exposure to benzene may result in bone marrow damage, which may be manifested initially as anemia, leukopenia, or thrombocytopenia. Continued exposures to benzene may result in aplastic anemia and progress to acute myelogenous leukemia (Cassarett & Doull, 1996).

Table G-2
Toxicity Summary for Acute Inhalation Exposures to Petroleum Products

Product	Species	Exp. Dur./Freq.	Dose Level	Effect	Notes	Reference
Gasoline	Rat		0.2 ml	Death	Aspiration	Gerarde, 1988
	Mouse	5 min.	120,000 mg/m^3	Death		Sandmeyer, 1984
	Human	1 hr.	2,250 mg/m^3	No Effects		Sandmeyer, 1984
	Human	1 hr.	3,680 mg/m^3	Slight dizziness, irritation to eyes, nose, throat		Sandmeyer, 1984
	Human	1 hr.	8,200 mg/m^3	Dizziness, mucous membrane irritation, anesthesia		Sandmeyer, 1984
Fuel Oils	Rat	1 d; 6 hr/d	4,000 mg/m^3	LC_{30}	unspecified diesel	Dalbey & Lock, 1983
	Rat	1 d; 6 hr/d	2,700 mg/m^3	NOAEL (death)	unspecified diesel	Dalbey & Lock, 1983
	Rat	10 d; 6 hr/d	400 ppm	NOAEL (body wt., food intake)	home heat, #2	Beliles & Mecler, 1983
	Rat	10 d; 6 hr/d	401.5 ppm	Decreased food intake	unspecified diesel	API, 1979
	Rat	10 d; 6 hr/d	408.8 ppm	NOAEL (body wt., food intake)	unspecified fuel oil	API, 1979
	Rat	10 d; 6 hr/d	400 ppm	NOAEL (developmental effects)	home heat, #2	Beliles & Mecler, 1983
	Rat	10 d; 6 hr/d	408.8 ppm	NOAEL (developmental effects)	unspecified fuel oil	API, 1979
	Rat	10 d; 6 hr/d	401.5 ppm	NOAEL (developmental effects)	unspecified diesel	API, 1979
	Mouse	5 d; 8 hr/d	135 mg/m^3	NOAEL (death)	fuel oil #2	Kainz & White, 1984
	Mouse	5 d; 8 hr/d	204 mg/m^3	LC_{30}	fuel oil #2	Kainz & White, 1984
	Mouse	5 d; 8 hr/d	135 mg/m^3	cardiovascular (vasodilation)	fuel oil #2	Kainz & White, 1984
	Mouse	5 d; 8 hr/d	135 mg/m^3	NOAEL (food consumption, body weight)	fuel oil #2	Kainz & White, 1984
	Mouse	5 d; 8 hr/d	204 mg/m^3	Decreased food & water intake, 30% weight loss	fuel oil #2	Kainz & White, 1984
	Mouse	5 d; 8 hr/d	65 mg/m^3	Ataxia, disturbed gait	fuel oil #2	Kainz & White, 1984

Table G-3
Toxicity Summary for Subchronic Inhalation Exposures to Petroleum Products

Product	Species	Exp. Dur./Freq.	Dose Level	Effect	Notes	Reference
Fuel Oils	Rat	13 wk; 4 h/d, 2d/wk	750 mg/m3	NOAEL (respiratory)	unspecified diesel	Dalbey et al, 1987
	Rat	13 wk; 4 h/d, 2d/wk	250 mg/m3	LOAEL (6-11% decrease in bodyweight)	unspecified diesel	Dalbey et al, 1987
	Rat	13 wk; 4 h/d, 2d/wk	1,500 mg/m3	LOAEL (increase in relative weight of right lobe of lung)	unspecified diesel	Dalbey et al, 1987
	Rat	13 wk; 6 h/d, 5d/wk	100 mg/m^3	NOAEL	kerosene	Carpenter et al, 1976
	Rat	13 wk; 6 h/d, 5d/wk	100 mg/m^3	NOAEL	kerosene	Carpenter et al, 1976
	Rat	13 wk; 4 h/d, 5d/wk	1,500 mg/m^3	NOAEL	unspecified diesel	Lock et al, 1984
	Rat	13 wk; 4 h/d, 2d/wk	250 mg/m^3	LOAEL	unspecified diesel	Lock et al, 1984
	Dog	13 wk; 6 h/d, 5d/wk	100 mg/m^3	NOAEL	kerosene	Carpenter et al, 1976

Epidemiological and case studies correlate benzene exposure with leukemia (ATSDR, 1996). USEPA has classified benzene as Group A based on several occupational exposures, as well as increased incidence of neoplasia in mice and rats (IRIS, 1994; USEPA, 1997). Evidence supports the hypothesis that more than one toxic effect contributes to the leukemogenic process, especially because benzene metabolites may be able to cause general disruption of protein functions in bone marrow cells, resulting in many effects. Data are not sufficient at this time to state which of the documented effects, genotoxic or non-genotoxic, are the critical ones for benzene-induced leukemogenicity (USEPA, 1997).

The available human data on the developmental and teratogenic effects of benzene vapors are inconclusive (NRC, 1996), although testicular lesions and ovarian cysts were observed in mice exposed to benzene at 300 ppm (Ward et al., 1985).

Acute Action Level

The Acute Action Level in air for benzene is 50 ppb (160 ug/m^3). This value is the acute inhalation Minimal Risk Level (MRL) derived by the Agency for Toxic Substances and Disease Registry and is based on studies demonstrating hematopoietic effects in animal systems. The MRL worksheet is included in Appendix H.

Subchronic Action Level

The Subchronic Action Level for benzene is 19 ppb (60ug/m^3). USEPA has derived this provisional subchronic inhalation RfC for benzene (HEAST, 1994) based on hematological and hematopoietic endpoints. We have adopted this subchronic RfC as the Subchronic Action Level for benzene. Its derivation is presented in Appendix H.

Chronic Action Level

The Chronic Action Level for benzene is 3 ppb (10 ug/m^3). The USEPA has derived both unit cancer risks and a provisional RfC for benzene. The unit cancer risk is 8.3E-6 per (ug/m^3). Assuming an Incremental Lifetime Cancer Risk of 1 in 100,000 (Maine Department of Environmental Protection, 1994), this is equivalent to 1 ug/m^3, or 0.3 ppb. USEPA's derivation of this value is presented in Appendix H. The provisional RfC for benzene of 0.5 ug/m^3, or 0.2 ppb is based on hematological effects (HEAST, 1995). The derivation of the RfC is presented in Appendix H. Both of these values are lower than the average background concentration for benzene in homes (see discussion of background concentrations in Section I of this report). Since it is not reasonable to set an Action Level that is lower than background, the Chronic Action Level is the background concentration for benzene in indoor air in residential buildings. As more data are collected, the background data set for benzene will become more robust.

Ethylbenzene

Toxicity Summary

The acute toxicity of ethylbenzene is low (NRC, 1996). The major effect associated with ethylbenzene vapors in humans is irritation of eyes, nose, and mucous membranes at concentrations of about 180 ppm (Bardodej and Cirek, 1988). There is some evidence of increased rates of skeletal malformations in rats exposed during gestation (days 7 to 15) to 138 ppm ethylbenzene (Unvary and Tatrai, 1985). Ethylbenzene did not elicit embryotoxicity, fetotoxicity, or teratogenicity in rabbits at 100 or 1000 ppm (Andrew et al., 1981). Wolf et al., (1956) exposed rats, guinea pigs, a rabbit, and monkeys to various concentrations of ethylbenzene for 7-8 hours/day, 5 days/week, for 186 days. In the rabbit and the monkey, 600 ppm induced slight histopathological changes in the epithelium of the testes. No testicular changes were identified in the rats or rabbits up to 2200 ppm. A 90-day subchronic study was conducted in F344/N rats and B6C3F1 mice exposed to 0, 100, 250, 500, 750, and 1000 ppm ethylbenzene by the National Toxicology Program (NTP, 1989; 1990). There were no exposure related clinical signs of toxicity or body weight in any of the exposed rats or mice. In rats, relative liver and kidney weights were increased in males and females at the 250 ppm and 500 ppm levels respectively. A two-year chronic assay under similar exposure conditions is currently being reviewed by NTP.

There are differences between the metabolism of ethylbenzene in rats and humans (Bardodej and Cirek, 1988) that may account for the inter-species toxicity differences. Although the study conditions for this conclusion were different, the major urinary metabolite in humans is mandelic acid, with no detectable levels of benzoic acid or 1-phenylethanol whereas in rats, mandelic acid, 1-phenylethanol, and benzoic acid are present in equal amounts. It should be noted that in rats, some of these metabolites are produced endogenously (NRC, 1996). It is not known whether the disposition of ethylbenzene in humans is more similar to that in the rabbit, monkey, or rat.

There is no evidence that ethylbenzene is genotoxic or carcinogenic (NRC, 1996). Ethylbenzene is classified as Group D based on a lack of bioassays and human studies (USEPA, 1991).

Acute Action Level

The Acute Action Level for ethylbenzene is 3,300 ppb (14,300 ug/m^3). This is based on the NOAEL of 100 ppm for developmental effects in Wistar rats exposed to 100 or 1,000 ppm ethylbenzene vapor 6 to 7 hours/day, 7 days/week during days 1-19 of gestation (Andrew et al., 1981). In this study, there was no effect on fertility in either group. The fetuses in the high exposure group had an increased incidence of supernumerary and rudimentary ribs. Absolute and relative liver, kidney, and spleen weights were significantly increased in pregnant rats in the high exposure group.

Derivation of Acute Level: MW = 106.18

$$NOAEL_{[HEC]} = NOAEL_{[ADJ]}\ (mg/m^3 \text{ or ppm}) \times [(V_A/BW)_A]/[(V_A/BW)_H]$$

where:

$NOAEL_{[ADJ]}$ = the NOAEL when considering developmental effects

$[(V_A/BW)_A]/[(V_A/BW)_H] = 1$ (Default blood:gas(air) partition coefficient of "1" for ethylbenzene was used)

$NOAEL_{[HEC]} = (NOAEL) \times 1$

$NOAEL_{[HEC]} = 434\ mg/m^3$

Uncertainty factors of "30" were used. A factor of "3" was applied to account for interspecies differences since the evidence for developmental effects is limited. There is no evidence of developmental effects in rabbits or mice and the disposition in rats is dissimilar to that in humans. A factor of "10" was applied to account for known human sensitivities to ethylbenzene.

$434\ mg/m^3/30 = 14.5\ mg/m^3 = 3.3$ ppm

The Acute Action Level for ethylbenzene is 3.3 ppm.

Subchronic Action Level

The Subchronic Action Level for ethylbenzene is 230 ppb (1,000 ug/m^3). USEPA has determined that the chronic RfC for ethylbenzene be adopted as the subchronic inhalation RfC (HEAST, 1994). The RfC is based on developmental toxicity endpoints in rabbits and rats. We have adopted this subchronic RfC as the Subchronic Action Level for ethylbenzene. Its derivation is presented in Appendix H.

Chronic Action Level

The Chronic Action Level for ethylbenzene is 230 ppb (1,000 ug/m^3). The USEPA has derived an inhalation RfC for ethylbenzene that is based on developmental toxicity endpoints in rabbits and rats (IRIS, 1991). We have adopted this RfC as the Chronic Action Level for ethylbenzene. Its derivation is presented in Appendix H.

n-Hexane

Toxicity Summary

In humans, sensorimotor polyneuropathy is the principal neurologic effect associated with inhalation exposures to n-hexane, although other effects include blurred vision, abnormal color vision, and cranial neuropathy (IRIS, 1991). The onset of symptoms may not occur until several months following the beginning the exposure. Affected individuals may recover completely following the removal from the exposure, although in severe cases individuals may retain some sensorimotor deficiencies. Results of an epidemiological study on two age-matched groups of workers exposed to 58 ppm n-hexane (and acetone) for an average of 6.2 years demonstrated no neurological abnormalities. However, neurophysiological tests showed significant differences in motor nerve conduction velocities and residual latency of motor nerve conduction between exposed and control workers (Sanagi et al.1980). The observed differences are consistent with n-hexane-induced peripheral neuropathy observed in other studies in humans and animals. The toxicity of n-hexane is due to its metabolite, 2,5-hexanedione (IRIS, 1991). This metabolite is also believed to be responsible for testicular atrophy in Sprague-Dawley rats exposed to 100 ppm n-hexane 18 hours/day, 7 days/week for 61 days (Nylen et al., 1989). It has been reported that 2,5-hexanedione disrupts Sertoli cell seminiferous tubule secretion as well as interfering with this cell's microtubular system (Richburg et al., 1994).

The Action Levels presented below are based on toxicity data derived from 99% pure hexane. The critical endpoints and toxic metabolite of n-hexane are well established. However, a compelling body of evidence is accumulating demonstrating that the use of n-hexane as the indicator for other compounds in the petroleum mixture may significantly over estimate the toxicity of the mixture (Edwards et al, 1997).

Acute Action Level

An Acute Action Level for n-hexane has not been developed at this time due to insufficient toxicological data.

Subchronic Action Level

The Subchronic Action Level for n-hexane is 108 ppb (400 ug/m^3). This value is based on a NOAEL of 500 ppm for epitheilial lesions in the nasal cavity of B6C3F1 mice following inhalation exposures to 0, 500, 1,000, or 10,000 ppm 99% pure n-hexane vapors for 6 hours/day, 5 days/week for 13 weeks (Dunnick et al., 1989).

Derivation of Subchronic Level: MW = 86.18

$NOAEL_{[HEC]} = NOAEL_{[ADJ]}$ (mg/m^3 or ppm) x $[(V_A/BW)_A]/[(V_A/BW)_H]$

Where:

NOAEL = 500 ppm = 1,762 mg/m^3

$NOAEL_{[ADJ]}$ (mg/m^3) = (1,762 mg/m^3) x (6 hrs/24 hrs) x (5 days/7 days) = 315 mg/m^3

The USEPA (IRIS, 1991) calculated the $NOAEL_{[HEC]}$ for a gas:respiratory effect in the extrathoracic region as follows: Mva = 0.04 cu.m/day, MVh = 20 cu.m/day, Sa(ET) = 2.9 sq. cm, Sh(ET) = 177 sq.cm. (Mva/Sa)/(MVh/Sh) = 0.122

$NOAEL_{[HEC]}$ = (315 mg/m^3) x (0.122)

$NOAEL_{[HEC]}$ = 38 mg/m^3

Uncertainty factors of "100" were used. A factor of "10" was applied to account for interspecies differences between rats and humans. A factor of "10" was applied to account for known human sensitivities to n-hexane.

38 mg/m^3/100 = 0.38 mg/m^3 = .108 ppm

The Subchronic Action Level for n-hexane is 108 ppb.

Chronic Action Level

The Chronic Action Level for hexane is 57 ppb (200 ug/m^3). The USEPA has derived an inhalation RfC for n-hexane that is based on the neurotoxicity of n-hexane in humans with supporting data in animals (IRIS, 1991). We have adopted this RfC as the Chronic Action Level for n-hexane. Its derivation is presented in Appendix H.

Naphthalene

Toxicity Summary

Effects of high dose exposures to naphthalene inhalation in humans include headache, confusion, eye irritation, nausea, profuse perspiration with vomiting, hematuria, and edema (NTP, 1992). Individuals with decreased glucose-6-phosphate dehydrogenase activity are particularly susceptible to hemolytic anemia following exposures to naphthalene (Cassarett & Doull, 1996). Hemolysis can lead to renal disease due to precipitated hemoglobin. 2-methylnaphthalene is less acutely toxic than naphthalene (Buckpitt and Franklin, 1989).

Male and female B6C3F1 mice exposed to 0, 10, or 30 ppm naphthalene vapor for 6 hours/day, 5 days/week, for 104 weeks showed dose-related chronic inflammation and metaplasia of the olfactory epithelium, hyperplasia of the respiratory epithelium in the

nose, and chronic inflammation in the lungs (NTP, 1992). The effects of single doses of naphthalene on the morphology of the bronchiolar epithelium contrasts with the results of experiments using multiple treatments. It appears that there is some tolerance observed after multiple doses of naphthalene (O'Brien et al., 1989).

Exposure of B6C3F1 mice to 0, 10, or 30 ppm naphthalene for 2 years resulted in an increased incidence of pulmonary alveolar/bronchiolar adenomas in female mice in the high dose group (NTP, 1992). Based on this finding, it was concluded that there is some evidence of carcinogenic activity of naphthalene.

Acute Action Level

An acute-duration inhalation toxicity-based level for naphthalene of 53 ppb was derived from a NOAEL value of 30 ppm for hematopoietic effects in mice (NTP, 1992). In this study, male and female B6C3F1 mice were exposed by inhalation to naphthalene at target concentrations of 0, 10, or 30 ppm. Exposures were for 6 hours daily, 5 days weekly, for 14 days. Hematological parameters examined included hematocrit, hemoglobin, erythrocytes, mean cell volume, reticulocytes, and leukocytes. A NOAEL of 30 ppm was identified from these evaluations.

Derivation of Acute Level:

$$NOAEL_{[HEC]} = NOAEL_{[ADJ]}\ (mg/m^3 \text{ or } ppm) \times [(V_A/BW)_A]/[(V_A/BW)_H]$$

Where:

NOAEL of 30 ppm is adjusted for continuous exposure

$$NOAEL_{[ADJ]} = 30\ ppm \times 6\ hrs/24/hrs \times 5\ days/7days$$

$$NOAEL_{[ADJ]} = 5.33\ ppm$$

Default blood:gas(air) partition coefficient of "1" for naphthalene was used due to lack of data.

$$NOAEL_{[HEC]} = (NOAEL_{[ADJ]}) \times 1$$

$$NOAEL_{[HEC]} = 5.33\ ppm$$

Uncertainty factors of "100" were used. A factor of "10" was applied to account for interspecies differences and a factor of "10" was applied to account for known human sensitivities to naphthalene.

5.33 ppm/100 = 53 ppb

The acute duration toxicity-based level is 53 ppb.

Subchronic Action Level

The Subchronic Action Level is 20 ppb (100 ug/m^3). By convention, we have modified the Chronic Action Level by a factor of "10" to account for a subchronic exposure duration. This is done due to the lack of subchronic inhalation studies.

The USEPA Pilot Program (USEPA ORD) is currently reviewing an RfC for naphthalene. A benchmark dose approach is being used in its derivation. It is expected that this value will appear in the IRIS database in late September, 1997. We recommend that the Subchronic Action Level be modified to reflect changes in the USEPA-derived RfC.

Chronic Action Level

The Chronic Action Level in air for naphthalene is 2 ppb (10 ug/m^3). We have adopted the chronic inhalation Minimal Risk Level (MRL) derived by ATSDR. This value is based on a LOAEL of 10 ppm for inflammation and hyperplasia of the lungs and respiratory passages in mice exposed to naphthalene vapors for two years (NTP, 1992). The ATSDR MRL worksheet is included in Appendix H.

The USEPA Pilot Program (USEPA ORD) is currently reviewing an RfC for naphthalene. A benchmark dose approach is being used in its derivation. It is expected that this value will appear in the IRIS database in late September, 1997. We recommend that the USEPA-derived RfC replace the current Chronic Action Level.

n-Nonane

Toxicity Summary

There is minimal data available on the toxicity of n-nonane. The toxicity of n-nonane vapor results in mucous membrane irritation and disruption of the CNS. The effects on the CNS are believed to be of lesser magnitude than those caused by shorter chain alkanes (Cassarett & Doull, 1986). Evidence of cerebellar dysfunction and damage to cerebellar neurons suggests that the CNS is the target organ for n-nonane toxicity (Nilsen et al., 1988). Harlan-Wistar rats exposed to 1,500 ppm n-nonane vapor for 6 hours/day for 7 days demonstrated increased salivation, slight coordination loss, irritation of eyes, and mild tremors. Rats exposed to 1,600 ppm n-nonane vapors for 6 hours/day, 5 days/week, for 13 weeks had significantly lower mean body weight gains than controls (Carpenter et al., 1978).

Acute Action Level

An Acute Action Level for n-nonane has not been developed at this time due to insufficient toxicological data.

Subchronic Action Level

The Subchronic Action Level for n-nonane is 1,000 ppb (5,250 ug/m^3). This Action Level is based on a study by Carpenter et al., 1978) in which male Harlan-Wistar rats were exposed to 360 ppm, 590 ppm, or 1,600 ppm n-nonane vapor for 6 hours/day, 5 days/week, for 13 weeks. The authors conclude that there were no lesions attibutable to inhalation of the vapor based on micropathological evaluation of the tissues. The only exposure-related effect was significantly lower mean body weights and body weight gains in rats subjected to 1,600 ppm n-nonane vapor. This study identifies a NOAEL of 590 ppm and a LOAEL of 1,600 ppm.

Derivation of Subchronic Level: MW = 128.26

$NOAEL_{[HEC]} = NOAEL_{[ADJ]}$ (mg/m^3 or ppm) x $[(V_A/BW)_A]/[(V_A/BW)_H]$

Where:

The NOAEL of 590 ppm is adjusted for continuous exposure

$NOAEL_{[ADJ]}$ = 590 ppm x 6 hrs /24hrs /day x 5 days /7 days /week

$NOAEL_{[ADJ]}$ = 104.7 ppm

Default blood:gas(air) partition coefficient of “1” for n-nonane was used due to lack of data.

$NOAEL_{[HEC]}$ = ($NOAEL_{[ADJ]}$) x 1

$NOAEL_{[HEC]}$ = 104.7 ppm

Uncertainty factors of “100” were used. A factor of “10” was applied to account for interspecies differences, and a factor of “10” was applied to account for known human sensitivities to n-nonane.

104.7 ppm /100 = 1.05 ppm = 1,000 ppb

The subchronic duration toxicity-based level is 1,000 ppb (5,250ug/m^3).

Chronic Action Level

The Chronic Action Level for n-nonane is 100 ppb (525 ug/m^3). The basis for this value is the same study that was used to derive the Subchronic Action Level. To derive the Chronic Action Level, an additional factor of "10" was applied to the Subchronic Action Level to account for a longer exposure duration.

Toluene

Toxicity Summary

Exposure to toluene vapor for short periods of time at 80-100 ppm results in local irritation to mucous membranes, dizziness, noise perception, and fatigue (NRC, 1996). Effects associated with exposure to toluene vapors for longer periods of time are predominantly on the central nervous system as measured at the cellular and molecular levels; receptor density and binding, protein phosphorylation, hormone responses, enzyme activity (MADEP, ORS; 1991). Chronic exposure to toluene has been shown to produce a dose and time-dependent irreversible progressive high frequency hearing loss in animals (Pryor et al., 1991). It appears that, unlike benzene, the major metabolic pathways for toluene produce products with lower toxicities that are readily excreted (Cassarett & Doull, 1996).

There are conflicting reports on the teratogenicity of toluene. In mice exposed to 400 ppm from gestation days 6-15 skeletal abnormalities were observed, while rats exposed to 399 ppm toluene for 24 hours/day during various portions of pregnancy was showed no teratogenic effects (reviewed in NRC, 1996). Continuous exposure to 266 ppm from gestation days 6-15 resulted in spontaneous abortion in rabbits, with a concomitant decrease in maternal weight gain (Ungvary and Tatrai, 1985). The ability of toluene to cause reproductive toxicity was studied by Taskinen et al., 1989. In this study, wives of men with high or frequent occupational exposures to toluene had an increased odds ratio of spontaneous abortion compared with controls, but there was no association with congenital malformations. The same authors demonstrated toluene to be negative in the Chernoff/Kavlock developmental toxicity assay in mice.

There is no evidence of carcinogenicity of toluene in F344 rats or B6C3F1 mice (NTP, 1989). There is very limited evidence of toluene genotoxicity.

Acute Action Level

The Acute Action Level for toluene is 4,000 ppb (15,080 ug/m^3). This is based on a study in which 16 individuals were exposed to 0, 10, 40, or 100 ppm toluene for 6 hours on each of 4 consecutive days (the exposure concentrations differed on each day). Individuals experienced eye and nose irritation at 100 ppm as well as headaches, dizziness, and a feeling of intoxication. These effects were not reported by the 10 or 40 ppm exposure groups. No effects were seen in performance tests at 10 or 40 ppm. This study indicates an NOAEL of 40 ppm (151 mg/m^3) and a LOAEL of 100 ppm (378 mg/m^3).

Derivation of Acute Level: MW = 92.15

$NOAEL_{[HEC]} = NOAEL_{[ADJ]}$ (mg/m^3 or ppm) x $[(V_A/BW)_A]/[(V_A/BW)_H]$

Where:

NOAEL = 151 mg/m^3

$[(V_A/BW)_A]/[(V_A/BW)_H]$ = 1 (Default blood:gas(air) partition coefficient of "1" for toluene was used)

$NOAEL_{[HEC]}$ = (NOAEL) x 1

$NOAEL_{[HEC]}$ = 151 mg/m^3

Uncertainty factors of "10" were used. A factor of "10" was applied to account for known human sensitivities to toluene.

151 mg/m^3/10 = 15.1 mg/m^3 = 4.0 ppm

The Acute Action Level for toluene is 4,000 ppb.

Subchronic Action Level

The Subchronic Action Level for toluene is 265 ppb (1,000 ug/m^3). USEPA has derived this provisional subchronic inhalation RfC for toluene (HEAST, 1994) based on neurochemical changes. We have adopted this subchronic RfC as the Subchronic Action Level for toluene. Its derivation is presented in Appendix H.

Chronic Action Level

The Chronic Action Level for toluene is 106 ppb (400 ug/m^3). The USEPA has derived an inhalation RfC for toluene that is based on neurological effects in humans and degeneration of the nasal epithelium in rats (IRIS, 1992). We have adopted this RfC as the Chronic Action Level for toluene. Its derivation is presented in Appendix H.

Xylenes

Toxicity Summary

When inhaled, xylene(s) cause CNS effects that at exposure concentrations of a few hundred parts per million may include irritation of the respiratory tract, headaches, dizziness, nausea, and tremors. At 5000 ppm, unconsciousness has been reported (Carpenter et al., 1975). Workers exposed to commercial xylene vapors in concentrations above 200 ppm have reported nausea, vomiting, heartburn, and loss of appetite (Browning, 1965). Inhalation exposures cause pulmonary edema and respiratory tract irritation. Animal studies suggest that xylenes may produce developmental effects that include delayed skeletal development and skeletal abnormalities, decreased fetal weight, and increased fetal death (Ungvary et al., 1980).

The National Toxicology Program found no evidence of carcinogenicity in studies of mixed xylenes in male and female F344/N rats administered 250 or 500 mg/kg xylenes via oral gavage with corn oil for 5 days/week for 103 weeks (NTP, 1986).

Acute Action Level

The Acute Action Level in air for xylene(s) is 1000 ppb (4,340 ug/m^3). We have adopted the acute inhalation Minimal Risk Level (MRL) derived by ATSDR. This value is based on a LOAEL of 100 ppm for increased reaction time in psychomotor tests in humans exposed to xylene vapors for 4 hours (Dudek et al., 1990). The ATSDR MRL worksheet is included in Appendix H.

Subchronic Action Level

The Subchronic Action Level in air for xylene(s) is 700 ppb (3,038 ug/m^3). We have adopted the subchronic inhalation Minimal Risk Level (MRL) derived by ATSDR. This value is based on a LOAEL of 200 ppm for developmental effects in rats exposed to xylene vapors for 6 hr/day during gestation days 4-20 (Hass and Jakobsen, 1993). The ATSDR MRL worksheet is included in Appendix H.

Chronic Action Level

The Chronic Action Level in air for xylene(s) is 100 ppb (434 ug/m^3). We have adopted the chronic inhalation Minimal Risk Level (MRL) derived by ATSDR. This value is based on a LOAEL of 100 ppm for neurological effects (increased prevelence of anxiety, forgetfulness, inability to concentrate) in humans exposed to xylene vapors for an average of 8 hours/day for 7 years (Uchida et al., 1993). The ATSDR MRL worksheet is included in Appendix H.

APPENDIX H - United States Environmental Protection Agency Integrated Risk Information System, Agency for Toxic Substances and Disease Registry, and Health Effects Assessment Summary Table Derivations of Toxicity-Based Action Levels

0276
Benzene; CASRN 71-43-2 (04/01/97)

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Benzene

File On-Line 03/01/88

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	02/01/94

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Benzene
CASRN -- 71-43-2

Not available at this time.

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Benzene
CASRN -- 71-43-2

Not available at this time.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Benzene
CASRN -- 71-43-2
Last Revised -- 02/01/94

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- A; human carcinogen

Basis -- Several studies of increased incidence of nonlymphocytic leukemia from occupational exposure, increased incidence of neoplasia in rats and mice exposed by inhalation and gavage, and some supporting data form the basis for this classification.

___II.A.2. HUMAN CARCINOGENICITY DATA

Aksoy et al. (1974) reported effects of benzene exposure among 28,500 Turkish workers employed in the shoe industry. Mean duration of employment was 9.7 years (1-15 year range) and mean age was 34.2 years. Peak exposure was reported to be 210-650 ppm. Twenty-six cases of leukemia and a total of

34 leukemias or preleukemias were observed, corresponding to an incidence of 13/100,000 (by comparison to 6/100,000 for the general population). A follow-up paper (Aksoy, 1980) reported eight additional cases of leukemia as well as evidence suggestive of increases in other malignancies.

In a retrospective cohort mortality study Infante et al. (1977a,b) examined leukemogenic effects of benzene exposure in 748 white males exposed while employed in the manufacturing of rubber products. Exposure occurred from 1940-1949, and vital statistics were obtained through 1975. A statistically significant increase (p less than or equal to 0.002) of leukemias was found by comparison to the general U.S. population. There was no evidence of solvent exposure other than benzene. Air concentrations were generally found to be below the recommended limits in effect during the study period.

In a subsequent retrospective cohort mortality study Rinsky et al. (1981) observed seven deaths from leukemia among 748 workers exposed to benzene and followed for at least 24 years (17,020 person-years). This increased incidence was statistically significant; standard mortality ratio (SMR) was 560. For the five leukemia deaths that occurred among workers with more than 5 years exposure, the SMR was 2100. Exposures (which ranged from 10-100 ppm 8-hour TWA) were described as less than the recommended standards for the time period of 1941-1969.

In an updated version of the Rinsky et al. (1981) study, the authors followed the same cohort to 12/31/81 (Rinsky et al., 1987). An in his earlier study, cumulative exposure was derived from historic air-sampling data or interpolated estimates based on exisitng data. Standardized mortality rates ranged from 109 at cumulative benzene exposures under 40 ppm-years and increased montonically to 6637 (6 cases) at 400 ppm-years or more. The authors found significantly elevated risks of leukemia at cumulative exposures less than the equivalent current standard for occupational exposure which is 10 ppm over a 40-year working lifetime.

Ott et al. (1978) observed three deaths from leukemia among 594 workers followed for at least 23 years in a retrospective cohort mortality study, but the increase was not statistically significant. Exposures ranged from <2 to >25 ppm 8-hour TWA.

Wong et al. (1983) reported on the mortality of male chemical workers who had been exposed to benzene for at least 6 months during the years 1946-1975. The study population of 4062 persons was drawn from seven chemical plants, and jobs were categorized as to peak exposure. Those with at least 3 days/week exposure (3036 subjects) were further categorizeed on the basis of an 8-hour TWA. The control subjects held jobs at the same plants for at least 6 months but were never subject to benzene exposure. Dose-dependent increases were seen in leukemia and lymphatic and hematopoietic cancer. The incidence of leukemia was responsible for the majority of the increase. It was noted that the significance of the increase is due largely to a less than expected incidence of neoplasia in the unexposed subjects.

Numerous other epidemiologic and case studies have reported an increased incidence or a causal relationship between leukemia and exposure to benzene

(IARC, 1982).

___II.A.3. ANIMAL CARCINOGENICITY DATA

Both gavage and inhalation exposure of rodents to benzene have resulted in development of neoplasia. Maltoni and Scarnato (1979) and Maltoni et al. (1983) administered benzene by gavage at dose levels of 0, 50, 250, and 500 mg/kg bw to 30-40 Sprague-Dawley rats/sex for life. Dose-related increased incidences of mammary tumors were seen in females and of Zymbal gland carcinomas, oral cavity carcinomas and leukemias/lymphomas in both sexes.

In an NTP (1986) study, benzene was administered by gavage doses of 0, 50, 100, or 200 mg/kg bw to 50 F344/N rats/sex or 0, 25, 50, or 100 mg/kg bw to 50 B6C3F1 mice/sex. Treatment was 5 times/week for 103 weeks. Significantly increased incidences ($p<0.05$) of various neoplasic growths were seen in both sexes of both species. Both male and female rats and mice had increased incidence of carcinomas of the Zymbal gland. Male and female rats had oral cavity tumors, and males showed increased incidences of skin tumors. Mice of both sexes had increased incidence of lymphomas and lung tumors. Males were observed to have harderian and preputial gland tumors and females had tumors of mammary gland and ovary. In general, the increased incidence was dose-related.

Slightly increased incidences of hematopoietic neoplasms were reported for male C57Bl mice exposed by inhalation to 300 ppm benzene 6 hours/day, 5 days/ week for 488 days. There was no increase in tumor incidence in male AKR or CD-1 mice similarly exposed to 100 ppm or 100 or 300 ppm benzene, respectively. Likewise male Sprague-Dawley rats exposed by inhalation to 300 ppm benzene were not observed to have increased incidence of neoplasia (Snyder et al., 1981).

Maltoni et al. (1983) treated male and female Sprague-Dawley rats in the following manner. Starting at 13 weeks of age rats were exposed to 200 ppm benzene 4 hours/day, 5 days/week for 7 weeks; 200 ppm 7 hours/day, 5 days/week for 12 weeks; 300 ppm 7 hours/day, 5 days/week for 85 weeks. An 8-hour/day TWA for 5 days/week was calculated to be 241 ppm. A statistically significant increase was noted in hepatomas and carcinomas of the Zymbal gland.

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Numerous investigators have found significant increases in chromosomal aberrations of bone marrow cells and peripheral lymphocytes from workers with exposure to benzene (IARC, 1982). Benzene also induced chromosomal aberrations in bone marrow cells from rabbits (Kissling and Speck, 1973), mice (Meyne and Legator, 1980) and rats (Anderson and Richardson, 1979). Several investigators have reported positive results for benzene in mouse micronucleus assays (Meyne and Legator, 1980). Benzene was not mutagenic in several bacterial and yeast systems, in the sex-linked recessive lethal mutation assay with Drosophila melanogaster or in mouse lymphoma cell forward mutation assay.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

___II.B.1. SUMMARY OF RISK ESTIMATES

Oral Slope Factor -- 2.9E-2 per (mg/kg)/day

Drinking Water Unit Risk -- 8.3E-7 per (ug/L)

Extrapolation Method -- One-hit (pooled data)

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	1E+2 ug/L
E-5 (1 in 100,000)	1E+1 ug/L
E-6 (1 in 1,000,000)	1E+0 ug/L

___II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Tumor Type -- leukemia
Test Animals -- human
Route -- inhalation, occupational exposure
Reference -- Rinsky et al., 1981; Ott et al., 1978; Wong et al., 1983

The slope factor was derived from human data for inhalation exposure (see dose-response data for inhalation quantitative estimate). The human respiratory rate was assumed to be 20 cu.m/day and the human drinking water intake was assumed to be 2 L/day. The fraction of the administered dose absorbed systemically via inhalation and via drinking water were assumed to be equal.

___II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

The unit risk estimate is the geometric mean of four ML point estimates using pooled data from the Rinsky et al. (1981) and Ott et al. (1978) studies, which was then adjusted for the results of the Wong et al. (1983) study as described in the additional comments section for inhalation data.

The unit risk should not be used if the water concentration exceeds 1E+4 ug/L, since above this concentration the unit risk may not be appropriate.

___II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

The pooled cohorts were sufficiently large and were followed for an adequate time period. The increases in leukemias were statistically significant and dose-related in one of the studies. Wong et al. (1983) disagrees that exposures reported in Rinsky et al. (1981) were within the recommended standards. For the five leukemia deaths in persons with 5 or more years exposure, the author notes that mean exposure levels (range 15-70 ppm) exceeded the recommended standard (25 ppm) in 75% of the work locations sampled. A total of 21 unit risk estimates were prepared using 6 models and various combinations of the epidemiologic data. These range over slightly more than one order of magnitude. A geometric mean of these estimates is 2.7E-2. Regression models give an estimate similar to the geometric mean.

The risk estimate above based on reconsideration of the Rinsky et al. (1981) and Ott et al. (1978) studies is very similar to that of 2.4E-2/ppm (cited in U.S. EPA, 1980) based on Infante et al. (1977a,b), Ott et al. (1978) and Aksoy et al. (1974). It was felt by the authors of U.S. EPA (1985) that the exposure assessment provided by Aksoy was too imprecise to warrant inclusion in the current risk estimate.

Risk estimates based on animal gavage studies are about 5 times higher than those derived from human data. Pharmacokinetic data which could impact the risk assessment are currently being evaluated.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

___II.C.1. SUMMARY OF RISK ESTIMATES

Inhalation Unit Risk -- 8.3E-6 per (ug/cu.m)

Extrapolation Method -- One-hit (pooled data)

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	1E+1 ug/cu.m
E-5 (1 in 100,000)	1E+0 ug/cu.m
E-6 (1 in 1,000,000)	1E-1 ug/cu.m

___II.C.2. DOSE-RESPONSE DATA FOR CARCINOGENICITY, INHALATION EXPOSURE

Tumor Type -- leukemia
Test Animals -- humans

Route -- inhalation, occupational exposure
Reference -- Rinsky et al., 1981; Ott et al., 1978; Wong et al., 1983

___II.C.3. ADDITIONAL COMMENTS (CARCINOGENICITY, INHALATION EXPOSURE)

The unit risk estimate is the geometric mean of four ML point estimates using pooled data from the Rinsky et al. (1981) and Ott et al. (1978) studies, which was then adjusted for the results of the Wong et al. (1983) study. The Rinsky data used were from an updated tape which reports one more case of leukemia than was published in 1981. Equal weight was given to cumulative dose and weighted cumulative dose exposure categories as well as to relative and absolute risk model forms. The results of the Wong et al. (1983) study were incorporated by assuming that the ratio of the Rinsky-Ott-Wong studies to the Rinsky-Ott studies for the relative risk cumulative dose model was the same as for other model-exposure category combinations and multiplying this ratio by the Rinsky-Ott geometric mean. The age-specific U.S. death rates for 1978 (the most current year available) were used for background leukemia and total death rates. It should be noted that a recently published paper (Rinsky et al., 1987) reported yet another case of leukemia from the study population.

The unit risk should not be used if the air concentration exceeds 100 ug/cu.m, since above this concentration the unit risk may not be appropriate.

___II.C.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, INHALATION EXPOSURE)

The pooled cohorts were sufficiently large and were followed for an ade quate time period. The increases in leukemias were statistically significant and dose-related in one of the studies. Wong et al. (1983) disagrees that exposures reported in Rinsky et al. (1981) were within the recommended standards. For the five leukemia deaths in persons with 5 or more years exposure, the author notes that mean exposure levels (range 15-70 ppm) exceeded the recommended standard (25 ppm) in 75% of the work locations sampled. The risk estimate above based on reconsideration of the Rinsky et al. (1981) and Ott et al. (1978) studies is very similar to that of 2.4E-2/ppm (cited in U.S. EPA, 1980) based on Infante et al. (1977a,b), Ott et al. (1978) and Aksoy et al. (1974). It was felt by the authors of U.S. EPA (1985) that the exposure assessment provided by Aksoy was too imprecise to warrant inclusion in the current risk estimate. A total of 21 unit risk estimates were prepared using 6 models and various combinations of the epidemiologic data. These range over slightly more than one order of magnitude. A geometric mean of these estimates is 2.7E-2/ppm. Regression models give an estimate similar to the geometric mean.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

Source Document -- U.S. EPA, 1980, 1985, 1987

The 1985 Interim Evaluation was reviewed by the Carcinogen Assessment Group.

The 1987 memorandum is an internal document.

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Work Group Review -- 03/05/87, 10/09/87

Verification Date -- 10/09/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX) or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

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_VI. BIBLIOGRAPHY

Substance Name -- Benzene
CASRN -- 71-43-2
Last Revised -- 03/01/90

__VI.A. ORAL RfD REFERENCES

None

__VI.B. INHALATION RfD REFERENCES

None

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Aksoy, M., S. Erdem and G. Dincol. 1974. Leukemia in shoeworkers exposed chronically to benzene. Blood. 44(6): 837-841.

Aksoy, M. 1980. Different types of malignancies due to occupational exposure to benzene: A review of recent observations in Turkey. Environ. Res. 23: 181.

Anderson, D. and C.R. Richardson. 1979. Chromosome gaps are associated with chemical mutagenesis (abstract No. Ec-9). Environ. Mutat. 1: 179.

IARC (International Agency for Research on Cancer). 1982. Benzene. In: Some industrial chemicals and dyestuffs. IARC Monographs on the evaluation of carcinogenic risk of chemicals to humans. IARC, WHO, Lyon, France. 29: 93-148.

Infante, P.F., R.A. Rinsky, J.K. Wagoner and R.J. Young. 1977a. Benzene and Leukemia. The Lancet. 2(8043): 867-869.

Infante, P.F., R.A. Rinsky, J.K. Wagoner and R.J. Young. 1977b. Leukemia in benzene workers. Lancet. 19: 76-78.

Kissling, M. and B. Speck. 1973. Chromosome aberrations in experimental benzene intoxication. HELV. Med. Acta. 36: 59-66.

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Maltoni, C., B. Conti and G. Cotti. 1983. Benzene: A multipotential carcinogen. Results of long-term bioassays performed at the Bologna Institute of Oncology. Am. J. Ind. Med. 4: 589-630.

Meyne, J. and M.S. Legator. 1980. Sex-related differences in cytogenetic effects of benzene in the bone marrow of Swiss mice. Environ. Mutat. 2: 43-50.

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Ott, M.G., J.C. Townsend, W.A. Fishbeck and R.A. Langner. 1978. Mortality among individuals occupationally exposed to benzene. Arch. Environ. Health. 33: 3-10.

Rinsky. R.A., R.J. Young and A.B. Smith. 1981. Leukemia in benzene workers. Am. J. Ind. Med. 2: 217-245.

Rinsky, R.A., A.B. Smith, R. Hornung, et al. 1987. Benzene and Leukemia. New England J. Med. 316(17): 1044-1050.

Snyder, C.A., M.N. Erlichman, S. Laskin, B.D. Goldstein, and R.E. Albert. 1981. The pharmacokinetics of repetitive benzene exposure at 300 and 100 ppm in AKR mice and Sprague-Dawley rats. Toxicol. Appl. Pharmacol. 57: 164-171.

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Benzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office (Cincinnati, OH) and Carcinogen Assessment Group (Washington, DC), and the Environmental Research Labs (Corvalis, OR; Duluth, MN; Gulf Breeze, FL) for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-018.

U.S. EPA. 1985. Interim Quantitative Cancer Unit Risk Estimates Due to Inhalation of Benzene. Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC for the Office of Air Quality Planning and Standards, Washington, DC.

U.S. EPA. 1987. Memorandum from J. Orme, HEB, CSD/ODW to C. Vogt, Criteria and Standards Division, ODW, June 1987.

Wong, O., R.W. Morgan and M.D. Whorton. 1983. Comments on the NIOSH study of leukemia in benzene workers. Technical report submitted to Gulf Canada, Ltd., by Environmental Health Associates.

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_VII. REVISION HISTORY

Substance Name -- Benzene
CASRN -- 71-43-2

Date	Section	Description
12/01/88	II.A.4.	Anderson and Richardson citation year corrected
12/01/88	II.A.4.	Kissling and Speck citation year corrected
07/01/89	I.B.	Inhalation RfD now under review
02/01/90	II.	Clarified citations
02/01/90	II.A.3.	Corrected Maltoni, 1979 to Maltoni and Scarnato, 1979
02/01/90	II.A.3.	Corrected Maltoni, 1983 to Maltoni et al., 1983
02/01/90	II.A.3.	Corrected Synder et al., 1980 to 1981
02/01/90	VI.	Bibliography on-line
03/01/90	VI.C.	Clarify Maltoni et al., 1983 and NTP, 1986 references
08/01/90	III.A.10	Primary contact changed
08/01/90	IV.F.1.	EPA contact changed
01/01/91	II.	Text edited
01/01/91	II.C.1.	Inhalation slope factor removed (global change)

01/01/92 IV. Regulatory actions updated
04/01/92 II.B.2. Text revised
02/01/94 II.D.3. Secondary contact's phone number changed

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SYNONYMS

Substance Name -- Benzene
CASRN -- 71-43-2
Last Revised -- 03/01/88

71-43-2
Benzene
benzol
coal naphtha
cyclohexatriene
phene
phenyl hydride
polystream
pyrobenzol

Benzene; Downloaded 8/13/97

Benzene; Downloaded 8/13/97

0051
Ethylbenzene; CASRN 100-41-4 (03/01/97)

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Ethylbenzene

File On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	06/01/91
Inhalation RfC Assessment (I.B.)	on-line	03/01/91
Carcinogenicity Assessment (II.)	on-line	08/01/91

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Ethylbenzene
CASRN -- 100-41-4
Last Revised -- 06/01/91

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this

substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Liver and kidney toxicity Rat Subchronic to Chronic Oral Bioassay Wolf et al., 1956	NOEL: 136 mg/kg/day (converted to 97.1 mg/kg/day) LOAEL: 408 mg/kg/day (converted to 291 mg/kg/day)	1000	1	1E-1

*Conversion Factors: 5 days/7 days; thus, 136 mg/kg/day x 5 days/7 days = 97.1 mg/kg/day

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Wolf, M.A., V.K. Rowe, D.D. McCollister, R.L. Hollingsworth and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzene. Arch. Ind. Health. 14: 387-398.

The chosen study is a rat 182-day oral bioassay in which ethylbenzene was given 5 days/week at doses of 13.6, 136, 408, or 680 mg/kg/day in olive oil gavage. There were 10 albino female rats/dose group and 20 controls.

The criteria considered in judging the toxic effects on the test animals were growth, mortality, appearance and behavior, hematologic findings, terminal concentration of urea nitrogen in the blood, final average organ and body weights, histopathologic findings, and bone marrow counts. The LOAEL of 408 mg/kg/day is associated with histopathologic changes in liver and kidney.

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF -- The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

MF --None

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

None.

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study -- Low
Data Base -- Low
RfD -- Low

Confidence in the chosen study is low because rats of only one sex were tested and the experiment was not of chronic duration. Confidence in the supporting data base is low because other oral toxicity data were not found. Low confidence in the RfD follows.

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

U.S. EPA. 1980. Ambient Water Quality Criteria for Ethylbenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-048. NTIS PB 81-117590.

U.S. EPA. 1985. Drinking Water Criteria Document for Ethylbenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. (Public review draft)

U.S. EPA. 1985. Health Effects Assessment for Ethylbenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. ECAO-CIN-H008.

The 1980 Ambient Water Quality Criteria Document for Ethylbenzene received extensive Agency and public review.

The 1985 Drinking Water Criteria Document for Ethylbenzene and the 1985 Health Effects Assessment for Ethylbenzene received extensive Agency review with the help of selected outside scientists.

Agency Work Group Review -- 05/20/85

Verification Date -- 05/20/85

___I.A.7. EPA CONTACTS (ORAL RfD)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX) or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Ethylbenzene
CASRN -- 100-41-4
Last Revised -- 03/01/91

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

___I.B.1. INHALATION RfC SUMMARY

Critical Effect	Exposures*	UF	MF	RfC
Developmental toxicity	NOAEL: 434 mg/cu.m (100 ppm) NOAEL(ADJ): 434 mg/cu.m	300	1	1E+0 mg/cu.m
Rat and Rabbit Developmental Inhalation Studies Andrew et al., 1981; Hardin et al., 1981	NOAEL(HEC): 434 mg/cu.m LOAEL: 4340 mg/cu.m (1000 ppm) LOAEL(ADJ): 4340 mg/cu.m LOAEL(HEC): 4340 mg/cu.m			

*Conversion Factors: MW = 106.18. Assuming 25C and 760 mmHg, NOAEL(mg/cu.m) = 100 ppm x MW/24.45 = 434 mg/cu.m. For developmental effects, this concentration is not adjusted; therefore, NOAEL(ADJ) = NOAEL. The NOAEL(HEC) was calculated for a gas:extrarespiratory effect, assuming periodicity was attained. Since b:a lambda values are unknown for the experimental animal species (a) and humans (h), a default value of 1.0 was used for this ratio. NOAEL(HEC) = NOAEL(ADJ) x (b:a lambda(a)/lambda(h)) = 434 mg/cu.m.

___I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

Andrew, F.D., R.L. Buschbom, W.C. Cannon, R.A. Miller, L.F. Montgomery, D.W. Phelps, et al. 1981. Teratologic assessment of ethylbenzene and 2-ethoxyethanol. Battelle Pacific Northwest Laboratory, Richland, WA. PB 83-208074., 108.

Hardin, B.D., G.P. Bond, M.R. Sikov, F.D. Andrew, R.P. Beliles and R.W. Niemeier. 1981. Testing of selected workplace chemicals for teratogenic potential. Scand. J. Work Environ. Health. 7(suppl 4): 66-75.

Inhalation experiments were conducted with Wistar rats (n=78-107/concentration) and New Zealand white rabbits (n=29-30/concentration) exposed 6 to 7 hours/day, 7 days/week during days 1-19 and 1-24 of gestation, respectively, to nominal concentrations of 0, 100, or 1000 ppm (434 or 4342 mg/cu.m) (Andrew et al., 1981). A separate group of rats was exposed pregestationally for 3 weeks prior to mating and exposure was continued into the gestational period. Actual concentrations were within 10% of target concentrations. All pregnant animals were sacrificed 1 day prior to term (21 days for rats; 30 days for rabbits). Maternal organs (liver, lungs, kidney, heart, spleen, adrenals, ovaries, and brain) were examined histopathologically. Uteri were examined and fetuses were weighed, sexed, and measured for crown-to-rump length, and examined for external, internal and skeletal abnormalities. For statistical analyses, the litter was chosen as the experimental unit.

Ethylbenzene did not elicit embryotoxicity, fetotoxicity, or teratogenicity in rabbits at either exposure level. There were no significant incidences of major malformations, minor anomalies, or common variants in fetal rabbits from exposed groups. Maternal toxicity in the rabbits was not evident. There was no evidence of histologic damage in any of the dams' organs. The principal observation noted by the investigators was a reduced number of live rabbit kits per litter ($p<0.05$) at both exposure levels when evaluated by ANOVA and Duncan's Multiple Range Test. The number of live kits per litter in the air-exposed controls was reported as 8 (3+/-s.d.), compared with 7 (3+/-s.d.) for each exposure group. However, if one recalculates the data presented in Table 9 of Andrew et al. (1981), the number of live kits per litter for the low concentration (100 ppm) was 8 rather than 7 as presented in the paper. Since the number of live kits per litter at the high concentration was 7, this may suggest an effect at 1000 ppm, but not at 100 ppm. However, the number of implantations per litter and the number of dead or resorbed per litter were not different from controls. Prenatal mortality ranged from 5 to 8% and preimplantation loss ranged from 18 to 27%. Neither indicated a concentration-related intrauterine mortality. The results of the rabbit study are indicative of a NOAEL of 100 ppm based on a lack of developmental effects in rabbits. The NOAEL(HEC) is 434 mg/cu.m.

In rats exposed only during gestation, there were no histopathological effects in any of the maternal organs examined. There was no effect on fertility or on any of the other measures of reproductive status. The principal observation in fetuses was an increased incidence ($p<0.05$) of supernumerary and rudimentary ribs in the high exposure group and an elevated incidence of extra ribs in both the high and 100 ppm groups. Both absolute

and relative liver, kidney, and spleen weights were significantly increased in pregnant rats from the 1000 ppm group.

Groups of female rats were also exposed for 3 weeks prior to mating and exposure was continued during gestation. Like the 1000-ppm group exposed only during gestation, there was also an increased incidence of extra ribs ($p<0.05$) in the pre-gestationally exposed high exposure group. However, an increased incidence was not seen at 100 ppm in those exposed pre-gestationally, in contrast to the comparable group exposed only during gestation. There was no increase in rudimentary ribs in either of exposed groups. When extra and rudimentary ribs were grouped together, there was no significant increase in supernumerary ribs in either of the exposed groups. The apparent discrepancy in the incidence of supernumerary ribs between the pregestationally-exposed group and those exposed only during gestation may be based, in part, on the fewer numbers of litters examined in the pregestationally-exposed group. There were no effects on fertility or on any of the of the other measures of reproductive status. No fetal toxicity was noted at either exposure level. Body weights, placental weights, and sex ratios were within normal limits. Absolute and relative liver and spleen weights were significantly increased in pregant rats from the 1000 ppm group; only relative kidney weight was increased significantly. There were no histopathological effects in any of the organs examined.

Skeletal variants were seen at both 434 and 4342 mg/cu.m in the rats with the effects at 432 mg/cu.m being reduced compared with those occurring at 4342 mg/cu.m. By themselves, the effects are marginally adverse, even at 4342 mg/cu.m. However, a weight-of-evidence approach, noting a cluster of other mild effects at 4342 mg/cu.m, is used to determine that 1000 ppm is a LOAEL. The skeletal variations are considered along with evidence of slightly reduced litter size in rabbits at 4342 mg/cu.m and an increase in "% skeletal retarded fetuses" at 600 mg/cu.m (Ungvary and Tatrai, 1985). Additional support for this position is derived from the observations of somewhat elevated maternal liver, kidney, and spleen weights (Andrew et al., 1981).

___I.B.3. UNCERTAINTY AND MODIFYING FACTORS (INHALATION RfC)

UF -- The uncertainty factor of 300 reflects a factor of 10 to protect unusually sensitive individuals, 3 to adjust for interspecies conversion and 10 to adjust for the absence of multigenerational reproductive and chronic studies.

MF -- None

___I.B.4. ADDITIONAL STUDIES / COMMENTS (INHALATION RfC)

Ungvary and Tatrai (1985) exposed CFY rats (n=17-20) to levels of 600, 1200, or 2400 mg/cu.m for 24 hours/day during days 7 to 15 of gestation. CFLP mice (n=20) were exposed to 500 mg/cu.m for 24 hours/day from gestational days 6 to 15 or for 3 days intermittently for 4 hours/day for days 6-15. It is not

clear from the description if the results pertain to the continuous exposure or the intermittent exposure. New Zealand rabbits (n=3-9) were exposed for 24 hours/day to concentrations of 500 or 1000 mg/cu.m from gestational days 7 to 20. Untreated animals and those exposed to air only served as controls.

It was stated that maternal toxicity (unspecified species) was moderate and concentration-dependent; however, no data were presented to support this statement. Maternal weight gain was reported to have decreased for rabbits exposed to 1000 mg/cu.m. It was reported that rabbits exposed to 1000 mg/cu.m exhibited mild maternal toxicity manifested by reduced weight gain. However, the percent weight gain was not reported. There were no data for developmental endpoints in the 1000-ppm group because there were no live fetuses. One dam had died and three others aborted in this exposure group. Four dams had total resorptions. However, four other compounds in addition to ethyl benzene were tested at 1000 mg/cu.m and all caused spontaneous abortions at this level. Thus, the results are not clearly indicative of a treatment-related effect. This observation, coupled with the lack of any indication of abortions in rabbits in the Hardin et al. (1981) study, suggests that this effect in rabbits is not treatment-related.

Ungvary and Tatrai (1985) did observe a significant reduction in the mean female fetal weight in rabbit dams exposed 24 hours/day to 500 mg/cu.m. Andrew et al. (1981) did not observe such an effect in rabbits exposed up to 4348 mg/cu.m. These conflicting results in rabbits might be attributable to differences in study design.

Postimplantation loss (% dead or resorbed fetuses), and exposure-related skeletal retardation were significantly elevated ($p<0.05$) in rats at all exposure levels with one exception. Exposure to 600 mg/cu.m for 6 hours/day (it was not stated if this was a single exposure or the exposure duration on each day of gestation) did not result in any statistically significant fetal effects although there was increased incidence of dead/resorbed fetuses, lower weight of fetuses, and skeletal retarded fetuses. In the 24-hour/day exposure groups, malformations characterized as "anomalies of the uropoietic apparatus" and an increased incidence of extra ribs were significantly increased only at the highest exposure level. No data were presented on the anomalies of the uropoeitic apparatus. There was a significant ($p<0.05$) increase in skeletal retardation and fetal resorption in all continuous exposure groups although the concentration-response was shallow. The percent skeletal retarded fetuses, for example, at exposure concentrations of 600, 1200, and 2400 mg/cu.m was 26, 30, and 35%, respectively; the incidence in controls was 13%. These results in rats suggest a LOAEL(HEC) of 2400 mg/cu.m for extra ribs in the absence of demonstrable maternal toxicity.

In mice, an increased incidence of "anomalies of the uropoietic apparatus" was the only observation, but no data were presented. There was no discussion concerning maternal toxicity.

A 90-day subchronic inhalation study was conducted in F344/N rats (n=10/sex/group) and B6C3F1 mice (n=10/sex/group) that were exposed to 0, 100, 250, 500, 750, and 1000 ppm (0, 434, 1086, 2171, 3257, and 4343 mg/cu.m) 6 hours/day, 5 days/week (NTP, 1988; 1989; 1990). The duration-adjusted values were 0, 77.5, 194, 388, 582, and 776 mg/cu.m, respectively. The test

atmosphere concentrations monitored by gas chromatography were within a 10% range of the target concentrations. At study termination, necropsies were conducted on the lung, liver, kideny, heart, testes, and thymus with organ weight measurements. Clinical chemistry data were obtained for rats. Histopathological examinations were conducted on all animals in the high concentration groups and in controls; animals in the lower concentration groups were evaluated when lesions were observed until no observed effects were seen. Sperm morphology and vaginal cytology tests were performed. There were no mortalities, exposure-related clinical signs of toxicity, or significant adverse effects on body weight in any of the exposed rats or mice.

In rats, hematology parameters were unaffected. Of the liver enzymes evaluated, only serum alkaline phosphatase (SAP) activity was significantly reduced in a concentration-related manner (at 500 ppm and above) for both sexes with a greater sensitivity in females. The significance of this decrease is not clear since in liver damage, SAP levels usually increase. The investigators suggested the decrease may be due to reduced water and food intake. No liver histopathology was noted for any exposure group. Significant concentration-related increases in absolute liver weights occurred in males at 250 ppm and higher (12.5, 17.3, 22.0, and 23.6% at 250, 500, 750, and 1000 ppm, respectively); in females the lowest concentration at which an increase in absolute liver weight was seen was in the 500-ppm group (11.8%). The increase in the 750- and 1000-ppm groups was 11.5 and 15.8%, respectively. Relative liver weights were significantly increased in all male exposure groups except the 100-ppm group while all female exposure groups except the two lowest groups showed significant increases. Absolute kidney weight in males significantly increased only in the 500- and 750-ppm groups; relative weight was increased in the three highest exposure groups. In females, both absolute and relative kidney weights increased significantly in the three highest exposure groups. Regeneration of renal tubules in the kidneys of male rats only was seen in all groups including controls. The severity of the lesions was greatest in the rats at in the high-exposure group.

The most significant gross observation in rats was the presence of enlarged bronchial and/or mediastinal lymph nodes, but these observations were not dose-related. The incidence for minimal lung inflammation in male rats was 0/10, 3/10, 9/10, 9/10, 8/10, and 10/10 for the 0-, 100-, 250-, 500-, 750-, and 1000-ppm exposure groups, respectively. Microscopically, this enlargement was attributable to an increase in normal constituents of the lymph nodes characterized by accumulations of macrophages, lymphocytes, neutrophils, and plasma cells. It was the opinion of the NTP Pathology Working Group (PWG) that hyperplasia of the lymph nodes and lower respiratory tract was typical of an infectious agent with an associated active immune response rather than ethylbenzene exposure (NTP, 1989). This diagnosis was supported by the following observations: an uneven distribution of lesions among and within groups; foci of airway inflammation were randomly distributed throughout the lungs; considerable variability in severity within groups; and there was no consistent concentration-response relationship. No lesions were seen in the nasal cavity. The PWG described these lesions as not typical of the type of lesions which occurs with known pulmonary irritants. These lesions were not found in control animals, which were housed in separate rooms. No infectious agent was identified upon serologic examination. In the draft NTP technical report (NTP, 1990), the inflammatory lung lesions were

described as probably unrelated to exposure. Antibodies to common rodent respiratory tract viruses were not detected. However, only sera from control rats were sampled. Lesions morphologically indistinguishable from those in this study have been seen in control and treatment groups of rats from other inhalation and dosed feed studies (NTP, 1990). The PWG recommended that this effect be reevaluated in another study.

In mice, no significant exposure-related gross or histopathological observations were noted at terminal necropsy of any organs, including the lung. The only exposure-related effects were significantly elevated absolute and relative liver weight in both sexes of mice at of 750 and 1000 ppm and significantly elevated relative kidney weight of the females exposed to 1000 ppm. There were no significant histopathological changes or function test alterations in either liver or kidney of either sex.

The NTP peer review of the subchronic study took place on November 20, 1990 at Research Triangle Park. The NTP Board of Scientific Counselors' panel of experts agreed with the conclusions of the NTP report that there were no indications of toxicity due to ethyl benzene. A 2-year lifetime study in both rats and mice has been initiated and exposures have been conducted through 7 months. No serial sacrifices are planned and results are not expected prior to 1992.

Clark (1983) exposed Wistar rats (n=18/sex/group) (12-13 weeks old) to 0 and 100 ppm (0 and 434 mg/cu.m) reagent grade ethylbenzene 6 hours/day, 5 days/week for 12 weeks. The duration-adjusted values were 0 and 77.5 mg/cu.m. Clinical observations, body weight, food intake, hematology, urinalysis, organ weights, and histopathology of all major organs (including the lung and nasal cavity) were used as parameters to assess toxicity. No statistically significant effects were observed at 100 ppm. There were no differences from controls in the liver enzymes, including SAP. While slight bile duct hyperplasia was seen in 15/18 exposed males and 14/18 exposed females, hyperplasia was also common in controls (10/18 females and 8/18 males), and these observations were not statistically significant. The results of this study suggest a NOAEL of 100 ppm. The NOAEL(HEC) is 77.5 mg/cu.m. The results are in general agreement with the findings of the NTP study in F344 rats.

Wolf et al. (1956) exposed rats (n=10-25/sex/group) to 400, 600 or 1250 ppm (1737, 2606, or 5428 mg/cu.m) ethylbenzene 7 hours/day, 5 days/week for about 6 months. The duration-adjusted values were 0, 362, 542, and 1131 mg/cu.m, respectively, using the 7-hour duration. Exposure ranged from 186 to 214 days. Male rats only were also exposed to 2200 ppm (9554 mg/cu.m) for 7 hours/day, 5 days/week for about 5 months. The duration-adjusted value was 1990 mg/cu.m. Histopathology was performed on a variety of organs including the lung. Data on liver and kidney weights and histopathology were not presented; these parameters were discussed only in descriptive terms. Repeated exposure of rats, guinea pigs, and rhesus monkeys was examined.

Growth was depressed moderately in male rats at 2200 ppm. Liver and kidney weights in rats were increased slightly in all exposed groups compared with matched controls, and rats exposed to 1250 and 2200 ppm developed histopathological changes manifested as cloudy swelling of the liver and renal

tubules and testicular degeneration. The date indicate a NOAEL for liver histopatholgy at 600 ppm (542 mg/cu.m). However, no incidence data was reported. Since it is not clear that these effects are adverse when taken in context with the results of the NTP study, a NOAEL or LOAEL is not identified.

Guinea pigs (5-10/sex/group) and rabbits (1-2/sex/group) were exposed to 0, 400, or 600 ppm (duration-adjusted concentrations of 0, 362, or 542 mg/cu.m, respectively) ethylbenzene 7 hours/day, 5 days/week for about 6 months. Only females were exposed to 1250 ppm (duration-adjusted value of 1131 mg/cu.m). Growth was depressed in female guinea pigs exposed to 1250 ppm. Liver weight was described as slightly increased only in the 600-ppm exposure group. The study does not clearly indicate 600 ppm as a LOAEL so the NOAEL for guinea pigs is designated at 600 ppm. The NOAEL(HEC) is 542 mg/cu.m. Other than an observation of slight degeneration of the testicular germinal epithelium in the male rabbit at 600 ppm, there were no adverse effects reported for rabbits of either sex.

One male Rhesus monkey was exposed to 600 ppm (duration-adjusted value of 542 mg/cu.m) and two females were exposed to 400 ppm (duration-adjusted value of 362 mg/cu.m). A slight degeneration of the testicular germinal epithelium and increased liver weight was observed in the male monkey. No effects were reported for the female rhesus monkeys.

The small number of rabbits and monkeys preclude identification of NOAEL and LOAEL values for these species.

Cragg et al. (1989) exposed B6C3F1 mice (n=5/sex/group) and F344 rats (n=5/sex/group) to actual concentrations of 0, 99, 382, and 782 ppm (0, 430, 1659, and 3396 mg/cu.m) 6 hours/day, 5 days/week for 4 weeks. The duration-adjusted values were 0, 77, 296, 606 mg/cu.m, respectively. In the same study, New Zealand White rabbits (n=5/sex/group) were exposed to actual concentrations of 0, 382, 782, or 1610 ppm (0, 1659, 3396, or 6992 mg/cu.m). The duration-adjusted values were 0, 296, 606 and 1249 mg/cu.m, respectively. No changes were evident in mortality, clinical chemistry parameters, urinalysis, nor were there treatment-related gross or histopathological findings. Urinalysis was not performed on rabbits and clinical chemistry parameters were not performed on mice. Liver enzymes measured included AP. Hematology was performed on all species. Histopathology was only conducted on the high concentration animals except all rabbits' testes were examined. There was no liver histopathology in any of the species.

In the 382-ppm exposure group, rats exhibited sporadic incidences of salivation and lacrimation. (These observations were not noted in the NTP subchronic study). Absolute liver weights were significantly increased in male rats; relative weight was increased at 782 ppm. In females, absolute liver weight was significantly increased at 782 ppm and relative weight at both concentrations. Male rats of the 782 ppm group had a significant ($p<0.05$) increase in platelets while females only had a significant ($p<0.05$) increase in total leukocytes.

In mice, females showed a statistically significant increase in absolute, but not relative liver weight, at 782 ppm. There were no significant liver weight changes in male mice. Both males and females exhibited an increased

liver weight relative to brain weight at 782 ppm only. Rabbits showed no changes in liver weight ratios at any exposure level.

Since there were no adverse histopathological findings for the liver, a NOAEL of 782 ppm is identified for rats and mice. The NOAEL(HEC) is 606 mg/cu.m. The NOAEL for rabbits is 1610 ppm; the NOAEL(HEC) is 1249 mg/cu.m.

Elovaara et al. (1985) found concentration-related increases in drug-metabolizing enzymes of liver and kidney, with corresponding ultrastructural alterations in a subchronic inhalation study with rats. Male Wistar rats (n=5/group) were exposed to 0, 50, 300, or 600 ppm (0, 217, 1302, or 2604 mg/cu.m) ethylbenzene 6 hours/day, 5 days/week for 2, 5, 9, or 16 weeks. The duration-adjusted values were 0, 38.7, 233, and 465 mg/cu.m, respectively. The liver was the only organ examined histologically (light and electron microscopy). There were no changes in liver weight at any concentration. After 16 weeks exposure, NADPH-cytochrome reductase and UDPG-transferase were significantly elevated at 300 and 600 ppm. Aminopyrine N-demethylase and 7-ethoxycoumarin-0-deethylase (7-ECDE) were elevated at all exposure levels. The elevation in UDPG-transferase was exposure-related and may signify glucuronidation of ethylbenzene metabolites during detoxication. Electron microscopy also showed changes in hepatocyte ultrastructure [e.g., smooth endoplasmic reticulum (SER) proliferation, slight degranulation of rough endoplasmic reticulum] at all exposure levels beginning 2 to 9 weeks after exposure. Necrosis was not observed nor were there any increases in serum alanine aminotransferase. SAP was not measured. The proliferation of SER is consistent with enzyme induction. At 16 weeks, changes in ultrastructure were mainly confined to the high-exposure group. There was no effect of exposure on hepatic glutathione (GSH) content. Significant increases in relative kidney weight only were reported following 2 and 9, but not at 16 weeks of exposure to 600 ppm. Kidney 7-ECDE, and UDPG transferase activities showed statistically significant and exposure-related increases at all exposure levels.

In the absence of histologic evidence of damage, changes in absolute or relative liver weight, and no effect on serum ALT, the microsmal enzyme induction and ultrastructural changes are considered to be adaptation phenomena. The results of this study suggest a NOAEL of 600 ppm. The NOAEL(HEC) is 465 mg/cu.m for liver and kidney. The absence of liver weight changes is not consistent with the findings of the NTP (1988) subchronic study.

Angerer and Wulf (1985) evaluated 35 workers who chronically (2-24 years, average 8.2 years) sprayed varnishes containing alkyd-phenol and polyester resins dissolved in solvent mixtures consisting principally of xylene isomers and ethylbenzene. Some of the varnishes contained lead-based pigments. The air samples from personal monitors indicated average levels of 4.0 ppm for ethylbenzene. Although workers had significantly elevated lymphocytes in addition to significantly decreased erythrocyte counts and hemoglobin levels compared with controls, these effects cannot be attributed to ethylbenzene since other compounds (e.g., xylene, methylchloroform, n-butanol, toluene, C9 hydrocarbons) were detected in some of the six workplaces evaluated.

Bardodej and Cirek (1988) carried out biomonitoring of 200 ethylbenzene

production workers occupationally exposed for a mean duration of 12.2 years to unspecified concentrations of ethylbenzene and benzene over a 20-year period. The workers were evaluated twice a year and ethylbenzene metabolites measured. No statistically significant differences in hematological effects (e.g., RBC, WBC, leukocyte and platelet counts) or liver function tests (e.g., aminotransferase and/or SAP and LDH activities and bilirubin tests) were observed between exposed and nonexposed workers.

___I.B.5. CONFIDENCE IN THE INHALATION RfC

Study -- Low
Data Base -- Low
RfC -- Low

The developmental study by Hardin et al. (1981) was well-conducted and indicated no clearly adverse effects in any species. The study is given a low confidence rating because higher exposure levels may have provided more information on the potential for maternal toxicity and developmental effects. The data base is given a low rating since although other studies have examined a variety of other endpoints (e.g., liver and lung), by histopathology in rats and mice, there are no chronic studies and no multi-generation developmental studies. These latter studies would be useful to determine more conclusively the potential of ethylbenzene to affect development.

NTP does not consider observations of lung lesions in rats exposed in the NTP subchronic study to be treatment-related. However, no infectious agent has been detected. Therefore, there remains a possibility that ethylbenzene may play a role in producing lung lesions. It is anticipated that this issue will be clarified upon completion of the chronic study in progress.

In view of the previous considerations, the RfC is given a low confidence rating.

___I.B.6. EPA DOCUMENTATION AND REVIEW OF THE INHALATION RfC

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- U.S. EPA, 1984; 1985; 1987

Agency Work Group Review -- 09/19/90, 12/20/90

Verification Date -- 12/20/90

___I.B.7. EPA CONTACTS (INHALATION RfC)

Please contact the Risk Information Hotline for all questions concerning this

assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX) or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Ethylbenzene
CASRN -- 100-41-4
Last Revised -- 08/01/91

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to human carcinogenicity.

Basis -- nonclassifiable due to lack of animal bioassays and human studies.

___II.A.2. HUMAN CARCINOGENICITY DATA

None.

___II.A.3. ANIMAL CARCINOGENICITY DATA

None. NTP has plans to initiate bioassay. Metabolism and excretion studies at 3.5, 35 and 350 mg/kg are to be conducted as well.

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

The metabolic pathways for humans and rodents are different (Engstrom et al., 1984). Major metabolites in humans, mandelic acid and phenylglyoxylic acid, are minor metabolites in rats and rabbits (Kiese and Lenk, 1974). The major animal metabolites were not detected in the urine of exposed workers (Engstrom et al., 1984).

Ethylbenzene at 0.4 mg/plate was not mutagenic for Salmonella strains TA98, TA1535, TA1537 and TA1538 with or without Aroclor 1254 induced rat liver homogenates (S9) (Nestmann et al., 1980). Ethylbenzene was shown to increase the mean number of sister chromatid exchanges in human whole blood lymphocyte culture at the highest dose examined without any metabolic activation system (Norppa and Vainio, 1983).

Dean et al. (1985) used a battery of short-term tests including bacterial mutation assays, mitotic gene conversion in Saccharomyces cerevisiae JD1 in the presence and absence of S9 and chromosomal damage in a cultured rat liver cell line. Ethylbenzene was not mutagenic in the range of concentrations tested (0.2, 2, 20, 50 and 200 ug/plate) for S. typhimurium TA98, TA100, TA1535, TA1537 and TA1538 or for Escherichia coli WP2 and WP2uvrA. Ethylbenzene also showed no response in the S. cerevisiae JD1 gene conversion assay. In contrast, ethylbenzene hydroperoxide showed positive responses with E. coli WP2 at 200 ug/plate in the presence of S9 and an equally significant response with the gene conversion system of yeast.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

Source Document -- U.S. EPA, 1980, 1984, 1987

The Ambient Water Quality Criteria Document and the Health Assessment Document have received Agency and external review. The Drinking Water Criteria Document has been extensively reviewed.

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Work Group Review -- 10/07/87

Verification Date -- 10/07/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX) or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

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CASRN -- 100-41-4
Last Revised -- 03/01/91

__VI.A. ORAL RfD REFERENCES

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__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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_VII. REVISION HISTORY

Substance Name -- Ethylbenzene
CASRN -- 100-41-4

Date	Section	Description
03/01/88	I.A.1.	Dose conversion clarified
03/01/88	I.A.6.	Documentation revised
03/01/88	III.A.	Health Advisory added
09/07/88	II.	Carcinogen summary on-line
08/01/89	VI.	Bibliography on-line
08/01/90	IV.F.1.	EPA contact changed
10/01/90	I.B.	Inhalation RfC now under review
03/01/91	I.B.	Inhalation RfC summary on-line
03/01/91	VI.B.	Inhalation RfC references added
06/01/91	I.A.7.	Primary contact changed
08/01/91	II.D.3.	Secondary contact changed
01/01/92	I.A.7.	Secondary contact changed
01/01/92	IV.	Regulatory actions updated

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SYNONYMS

Substance Name -- Ethylbenzene
CASRN -- 100-41-4
Last Revised -- 01/31/87

100-41-4
AETHYLBENZOL
BENZENE, ETHYL
EB
ETHYLBENZEEN
Ethylbenzene
ETHYLBENZOL
ETILBENZENE
ETYLOBENZEN
NCI-C56393
PHENYLETHANE
UN 1175

Ethylbenzene; Downloaded 8/13/97

Ethylbenzene; Downloaded 8/13/97

0545
Methyl tert-butyl ether (MTBE); CASRN 1634-04-4 (04/01/97)

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR MTBE

File On-Line 12/01/91

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	03/01/93
Inhalation RfC Assessment (I.B.)	on-line	09/01/93
Carcinogenicity Assessment (II.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Methyl tert-butyl ether (MTBE)
CASRN -- 1634-04-4

Not available at this time.

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Methyl tert-butyl ether (MTBE)
CASRN -- 1634-04-4

Last Revised -- 09/01/93

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

___I.B.1. INHALATION RfC SUMMARY

Critical Effect	Exposures*	UF	MF	RfC
Increased absolute and relative liver and kidney weights and increased severity of spontaneous renal lesions (females), increased prostration (females), and swollen periocular tissue (males and females)	NOAEL: 1453 mg/cu.m (403 ppm) NOAEL(ADJ): 259 mg/cu.m NOAEL(HEC): 259 mg/cu.m LOAEL: 10899 mg/cu.m (3023 ppm) LOAEL(ADJ): 1946 mg/cu.m LOAEL(HEC): 1946 mg/cu.m	100	1	3E+0 mg/cu.m

Chronic Rat 24-Month Inhalation Study

Chun et al., 1992

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*Conversion Factors and Assumptions -- MW = 88.15. Assuming 25 C and 760 mmHg, NOAEL(mg/cu.m) = 403 ppm x 88.15/24.45 = 1453. NOAEL(ADJ) = 1453 x 6 hours/24 hours x 5 days/7 days = 259 mg/cu.m. The NOAEL(HEC) was calculated for a gas:extrarespiratory effect in rats assuming periodicity was attained. Because the b:a lambda values are unknown for the experimental species (a) and humans (h), a default value of 1.0 is used for this ratio. NOAEL(HEC) = NOAEL(ADJ) x [b:a lambda(a)/b:a lambda(h)] = 259 mg/cu.m.

___I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

Chun, J.S., H.D. Burleigh-Flayer, and W.J. Kintigh. 1992. Methyl tertiary butyl ether: vapor inhalation oncogenicity study in Fischer 344 rats (unpublished material). Prepared for the MTBE Committee by Bushy Run Research Center, Union Carbide Chemicals and Plastics Company Inc. Docket No. OPTS-42098.

In a chronic inhalation study (Chun et al., 1992), Fischer 344 rats (50 males, 50 females/group) were exposed to analytical mean concentrations of 403, 3023, or 7977 ppm methyl tertiary-butyl ether (MTBE) vapors (1453, 10,899, or 28,760 mg/cu.m) 6 hours/day, 5 days/week for 24 months (duration-adjusted values are 259, 1946, and 5136 mg/cu.m, respectively). The control animals breathed air. Hematology (all rats) was performed halfway through the experiment (control and high-concentration groups) and prior to final sacrifice (all groups). Blood and urine samples were collected and stored, but complete serum chemistry and urinalysis were not performed. Corticosterone levels were measured on 10 rats/sex/group prior to sacrifice. Clinical signs, body weights, organ weights, and food consumption were monitored. Complete necropsy and histopathology, including examination of the nasal turbinates and lower respiratory tract, were performed on all animals.

Survival times for females were not significantly different between exposed and control rats. A slight decrease in mean survival time was observed in the males exposed to the low concentration (controls, 632 days; low-concentration group, 617 days; $p < 0.05$). Survival time clearly decreased in males exposed to both the mid and high concentrations (mid-concentration group, 587 days; high-concentration group, 516 days; $p < 0.01$), leading to earlier sacrifice times at 97 and 82 weeks, respectively. According to study pathologists, chronic, progressive nephropathy was the main cause of death in the higher concentration groups and also contributed to a slight increase in mortality in the males exposed to the low concentration (Garman, 1993a,b). In NTP oral and inhalation 2-year studies of other compounds that exacerbate rat chronic, progressive nephropathy (e.g., 1,4-dichlorobenzene, dimethyl methylphosphonate, hexachloroethane, isophorone, pentachloroethane, tetrachloroethylene, chlorothalonil, and trichloroethylene), survival rates in male rats have been low, particularly in the high-dose groups (U.S. EPA, 1991). As with MTBE, decreased survival of male rats exposed to dimethyl methylphoshponate was attributed, at least in part, to chemically related kidney toxicity (i.e., nephropathy) (NTP, 1987).

For animals exposed to the high concentration, clinical signs that were markedly increased over controls were ataxia (2-4% of controls at end of study vs. 100% of males and females at high-exposure level starting day 2) and earlier onset and increased incidence of swollen periocular tissue (<50% of controls at end of study vs. 84% of males and 100% of females starting day 12). The observation of ataxia at this exposure level is consistent with findings from the subchronic study discussed below (Dodd and Kintigh, 1989). Increased salivation was observed in males only at the high-exposure level. At the mid-concentration level, the authors did not report increased ataxia, but an increase in incidence of prostration was observed in females (6/50 controls vs. 15/50 at the mid concentration). Early onset and increased incidence of swollen periocular tissue were also reported at the mid-

concentration level (68% of males and 100% of females starting days 12 and 19, respectively). Swollen periocular tissue, salivation, and prostration were not reported at any exposure level in the subchronic study (Dodd and Kintigh, 1989).

As is discussed in Section I.B.4., the corresponding subchronic study by Dodd and Kintigh (1989) assessed several neurological endpoints, including pathological examinations, brain size parameters, and functional observational batteries (FOBs). The only CNS effect found in the subchronic study at the 4000-ppm level was a slight decrease in brain length of the male rats ($p < 0.05$). Significant ($p < 0.05$) decreases in absolute brain weights of 8000-ppm males and females supported the use of this endpoint as a critical effect for derivation of the previously reported MTBE RfC, which was based on these 90-day study data. The chronic study did not measure brain length as a parameter, but did assess brain weight. The lack of brain length measurements in the chronic study is not considered a major study deficit because no significant differences in male or female brain weights were observed at any chronic exposure level.

As was observed in the subchronic study (Dodd and Kintigh, 1989), body weight gain and absolute body weight were decreased in both sexes of the high-concentration group. Just prior to sacrifice at week 81, body weight gain and absolute body weight in males were decreased 29 and 19%, respectively. Body weight gain and absolute body weight in females were decreased 22 and 13%, respectively, at the end of the study. Exposure-related, 18-25% increases in kidney and liver weights (absolute and relative to body and brain weights) were reported in females in the mid- and high-exposure groups ($p < 0.01$). No significant increases in liver or kidney weights were observed in the male rats.

No concentration-related histopathologic findings were reported in the livers of either sex. Increased incidence of hepatocellular hypertrophy (males) and degeneration (females) were observed in animals exposed to the mid concentration, but not the high concentration. No treatment-related lesions were observed in the respiratory tract in any group. Similarly, no pathologic changes were reported in the corresponding subchronic study by Dodd and Kintigh (1989).

Increases in microscopic kidney changes indicative of chronic nephropathy were seen in a concentration-related manner in all groups of exposed male rats and, to a lesser extent, in females exposed to the mid and high MTBE concentrations. Increases in the severity of mineralization and interstitial fibrosis were observed at all chronic-exposure concentrations in the male rats. Increased mineralization was not observed in females, but increases in mild to moderate glomerulosclerosis and interstitial fibrosis and tubular proteinosis were observed at the mid- and high-exposure levels in the female rats.

U.S. EPA (1991) clearly indicates that nephropathy in male rats associated with the induction of alpha-2u-globulin (a male-rat-specific protein) accumulation in hyaline droplets (located in the P2 segment of the proximal tubule cells of the kidneys) "is not an appropriate endpoint to determine noncancer (systemic) effects potentially occurring in humans." U.S. EPA

(1991) further outlines the following criteria for identification of an alpha-2u-globulin toxicant: (1) increased number and size of hyaline droplets in renal proximal tubule cells of treated male rats, (2) the accumulating protein in the hyaline droplets is alpha 2u globulin, and (3) additional aspects of pathological sequence of lesions associated with alpha-2u-globulin nephropathy are present, as described in U.S. EPA (1991). For reasons discussed below, the nephropathy in the male rats (and the associated decreased survival time) is thought to be at least partially due to alpha-2u-globulin accumulation, confounding the results of the male rat chronic bioassay and precluding its use as a basis for a quantitative determination of human noncancer risk.

The first criterium listed above was addressed in the subchronic study by Dodd and Kintigh (1989). They reported that slides of kidney sections from five male rats in each treatment group and from five female rats from the high-level (7977-ppm) treatment group were independently "blind" evaluated by three pathologists for treatment-related differences in hyaline droplet formation. The average grades for extent of hyaline droplet formation based on a scale ranging from 0 (no findings) to 5 (severe) were 0 for the female rats exposed to 7977 ppm and 2.56, 1.94, 3.06, and 3.66 for the control and 800-, 4000-, and 7977-ppm males, respectively. Thus, these results indicate no hyaline droplet formation in female rats and a moderate (one-grade) increase in hyaline droplet formation for male rats at the high-exposure level. Further, hyaline droplet increases at the high dose were observed in a subchronic gavage study (Robinson et al., 1990) and in a subchronic drinking-water study (Lindamood et al., 1992) of male Fischer 344 rats exposed to tert-butyl alcohol (TBA), the principal metabolite of MTBE.

The second criterium, alpha-2u-globulin levels in the hyaline droplets, was addressed in a separate analysis of male rats from the subject subchronic study (Swenberg and Dietrich, 1991). Although they were not increased in a concentration-related manner, Swenberg and Dietrich (1991) observed an approximate doubling in the percentage of renal cortex staining for alpha 2u globulin in all male rat exposure groups of the subchronic study. Although the pattern of alpha-2u-globulin accumulation is not consistent with other known alpha-2u-globulin toxicants (e.g., limonene), these results suggest that the aforementioned increase in hyaline droplet formation could, at least partially, be due to the accumulation of this male-rat-specific protein.

Finally, subchronic and chronic inhalation studies reveal that MTBE does induce most of the pathologic progression (from hyaline droplet formation to acceleration of chronic progressive nephropathy to renal tubular cell tumors) identified as characteristic of alpha-2u-globulin-type toxicity (U.S. EPA 1991). Swenberg and Dietrich (1991) reported that alpha-2u-globulin-positive proteinaceous casts at the junction of the proximal tubules and the thin limb of Henle were not observed. However, Robinson et al. (1990) found that 50% of male Sprague-Dawley rats orally dosed with 1200 mg MTBE/kg displayed "small numbers of tubules which were plugged with granular casts." Further, granular casts at this part of the nephron can lead to subsequent tubular dilation (U.S. EPA, 1991), an effect that was noted in the chronically exposed male (1/50, 13/50, 14/50, and 11/50 in control and low-, mid-, and high-exposure groups, respectively), but not female (2/50, 0/50, 3/50, and 3/50 in control, low-, mid-, and high-exposure groups, respectively) rats (Chun et al., 1992). The reason this pathology was not observed following the 90-day study is not

known at this time but may be related to differences in test species strain or due to differences resulting from differing administration routes.

Another indication that MTBE exacerbation of chronic progressive nephropathy (CPN) may be related to alpha 2u globulin is that MTBE accelerates CPN to a much lesser degree in animals that can not produce alpha 2u globulin (i.e., female rats, all mice). The graded kidney lesion responses observed in male and female rats (Tables 40 and 45) were analyzed by logistic regression models to determine the extent to which MTBE impacted male and female kidneys differently. Males and females differed significantly with respect to concentration-response slopes for interstitial nephritis ($p < 0.025$), interstitial fibrosis ($p < 0.005$), and mineralization ($p < 0.005$), but not with respect to tubular proteinosis ($p > 0.1$) and glomerulosclerosis ($p > 0.1$) (Allen, 1993). In all cases where the slopes differed significantly, the slope for males was greater than the slope for females.

As with the male rats, the nephropathy present in the female MTBE-exposed rats did not differ histologically from the "spontaneous" nephropathy common in older Fischer 344 rats. The heightened degrees of nephropathy seen in relation to the MTBE exposures represent an exacerbation of this spontaneous rat nephropathy (Garman, 1993a). Of the observed kidney lesions, the study pathologist's diagnosis of tubular proteinosis was considered most representative of overall nephropathy (Garman, 1993b). An analysis of the average severity grade for these lesions in the different exposure groups (where 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, and 5 = severe) revealed scores of 2.8, 2.8, 3.8, and 3.5 for females sacrificed at 24 months in the control group and 403-, 3023-, and 7977-ppm exposure groups, respectively (Eldridge, 1993). Trend analyses (using methods described by Tukey et al., 1985) of this and other kidney lesions confirm the 403-ppm NOAEL and 3023-ppm LOAEL with respect to renal effects in the female rats (Allen, 1993). In males, 403-ppm was determined to be a NOAEL for interstitial nephritis, tubular proteinosis, and glomerulosclerosis, and a LOAEL for mineralization and interstitial fibrosis. The 403-ppm NOAEL for renal effects in the female rats was also confirmed via a blinded reevaluation of the original kidney slides by a second pathologist (Busey, 1993).

In summary, there is some evidence for alpha-2u-globulin nephropathy in male rats. This limited evidence, however, is sufficient to eliminate male rat kidney nephropathy as a possible critical endpoint for use in the derivation of an RfC. Also, the induction of nephropathy in females indicates that MTBE induces renal pathology by more than one mechanism. Because the female rat lacks alpha 2u globulin, the mechanism of pathologic induction is not considered to be unique, and renal pathology in females is thus considered to be suitable for use in the development of an RfC.

Exposure to MTBE vapor for 24 months produced various signs of toxicity in female rats exposed to 3023 ppm MTBE, including prostration, swollen periocular tissue, increased relative and absolute liver and kidney weights, and increased severity of certain renal lesions. Thus, 3023 ppm was a LOAEL [LOAEL(HEC) = 1946 mg/cu.m], and 403 ppm [NOAEL(HEC) = 259 mg/cu.m] was a NOAEL for chronic exposure to female rats.

A two-generation reproduction study (Neeper-Bradley, 1991) of Sprague-

Dawley rats lends support to the NOAEL level determined in the Chun et. al. (1992) chronic study. In accordance with current U.S. EPA risk assessment policy, no adjustment is made to approximate an equivalent continuous exposure level for developmental endpoints (U.S. EPA, 1989a). As a result, the NOAEL(HEC) for this developmental endpoint is higher than the NOAEL(HEC) derived from the Chun et al. (1992) study.

Neeper-Bradley (1991) conducted a two-generation reproduction study in CD (Sprague-Dawley) rats. Male and female rats were exposed to mean MTBE concentrations of 0, 402, 3019, and 8007 ppm over two generations. F0 animals, 25/sex/concentration, were exposed for 10 weeks and then bred once to produce F1 litters. Twenty-five pups/sex/group from the F1 generation were selected randomly to be parents of the F2 generation and were exposed for at least 8 weeks prior to mating. Exposures continued through mating, through day 19 of gestation, and from lactation days 5-28 for both generations of parents. The rats were exposed for 6 hours/day, 5 days/week during the prebreeding exposure period and for 7 days/week during mating, gestation, and postnatal periods. The approximate age of the F0 animals at the start of prebreeding exposures was 6 weeks. Prebreeding exposures for the selected F1 weanlings began 29-31 days from birth. Parental animals were monitored for clinical signs of toxicity, food consumption, and body weight. All F0 and F1 parents were necropsied and examined for gross lesions; liver weights of F1 parents were measured at necropsy. Upper and lower respiratory tracts and selected reproductive tissues from the high-concentration and control groups were examined histologically, as were tissues with gross lesions. Offspring were evaluated for viability, survival, body weight, and sex distribution.

Prebreeding exposures of 7977 ppm resulted in reduced food consumption during the first 2-3 weeks (F0 and F1 males) and body weight and body weight gain reductions throughout the exposure period (F0 and F1 males and F1 females). Other signs of parental toxicity at 7977 ppm included perioral wetness, hypoactivity, lack of startle reflex, ataxia, blepharospasm, and increased relative liver weights (F1 generation only). At 3023 ppm, adult effects included hypoactivity, lack of startle reflex, blepharospasm, increased relative liver weights (F1 males only), and transient reductions in body weight (F1 males and females). The histopathologic evaluation revealed no exposure-related lesions in the organs examined from males and females of either parental generation. The NOAEL and LOAEL for paternal effects in this study were 403 and 3023 ppm, respectively, which support the effect levels designated for the principal study (Chun et al., 1992).

Mating, fertility, and gestational indices were not adversely affected in either of the two parental generations. Body weights, weight gains, and food consumption were similar for treated and control groups throughout gestation. However, maternal exposure to 3023 and 7977 ppm resulted in statistically significant reduced body weights and reduced body weight gains in F1 pups ($p < 0.05$ at 3023 ppm; $p < 0.01$ at 7977 ppm) and F2 pups ($p < 0.01$ for both exposure groups), principally during the latter periods of lactation. A significant ($p < 0.01$) decrease in pup survival in the F1 litter on lactation days 0-4 (precull) for the 7977-ppm exposure group (91.5% survival, 259/283) compared with controls (98.6%, 289/293) was attributed to the loss of an entire litter (16 pups). The authors state that this loss was not related to MTBE toxicity, but no further explanation is provided. In the 7977-ppm F2

litters, pup survival was reduced on postnatal day 4 (93.5% survival, 275/294) compared with controls (98.1%, 305/311). A NOAEL of 403 ppm [1442 mg/cu.m; NOAEL(HEC) = 1442 mg/cu.m] and a LOAEL of 3023 ppm (10,816 mg/cu.m) for reduced body weight and body weight gain in both F1 and F2 pups during postnatal development (lactation period) were determined.

Biles et al. (1987) conducted a one-generation reproductive toxicity investigation. Sprague-Dawley rats (15 males, 30 females/group) were exposed to MTBE concentrations of 0, 290, 1180, and 2860 ppm (0, 1046, 4254, and 10,311 mg/cu.m) (males) and 0, 300, 1240, and 2980 ppm (0, 1082, 4470, and 10,743 mg/cu.m) (females), 6 hours/day, 5 days/week, during the premating interval (12 weeks for males, 3 weeks for females). There were two 5-day mating intervals (two females for every male). Males (F0 generation) continued to be exposed during and between matings, whereas F0 females were exposed 7 days/week on days 0-21 of gestation and 5 days/week on days 5-20 of lactation. After unexposed litters (F1a) were weaned, the F0 males and F0 females underwent another mating period with the same exposure regimen to produce a second litter (F1b). F0 males were sacrificed after this mating period, and females were sacrificed after the end of F1b weaning. Thus, F0 males were exposed overall to MTBE for approximately 28 weeks, and F0 females were exposed for 16 weeks. These animals were examined for gross changes, especially in their reproductive organs. Histopathologic examination revealed an increased incidence of dilated renal pelves in females exposed to 300 (4/30, 13%) and 2980 ppm (5/30, 17%) compared with controls (1/30, 3%). However, this finding was not observed at the mid concentration of 1240 ppm (0/30, 0%), which preclude establishing an unequivocal concentration-response relationship. The pregnancy rate was not significantly affected in either mating interval (F1a and F1b), although the F1b matings were slightly reduced in the high-exposure group (18/25, 76%) compared with controls (22/25, 88%). On day 4 of lactation, each litter with greater than 10 pups was culled. Pups were sacrificed on day 21 of lactation. The pup viability indices at birth were slightly, but significantly, decreased ($p < 0.05$) in the F1b litters of the dams exposed to 1240 (95.5% viability, 278/291) and 2980 ppm (95.5% viability, 234/245) compared with litters of controls (99% viability, 292/295). The F1a litter's pup viability indices did not differ from controls. Pup survival in the F1a litter was significantly decreased ($p < 0.01$) on lactation days 0-4 (precull) for the 300- (91.4% survival, 317/347) and 1240-ppm (89.1% survival, 205/230) exposure groups compared with controls (98.2% survival, 324/330). However, the F1a high-exposure group displayed no reduction in pup survival when compared to controls, and no reduction in pup survival was seen in the F1b litters. Further, pup survival indices for lactation days 4-21 (post-cull) were not increased over controls. Consequently, the reduced pup survival in the F1a low- and mid-exposure groups is not believed to be a treatment-related effect. A NOAEL of 300 ppm [1082 mg/cu.m; NOAEL(HEC) = 1082 mg/cu.m] and a LOAEL of 1240 ppm (4470 mg/cu.m) (female rats) for decreased pup viability in F1b litters were determined.

___I.B.3. UNCERTAINTY AND MODIFYING FACTORS (INHALATION RfC)

UF -- An uncertainty factor of 10 is applied to account for extrapolation to sensitive human subpopulations. An additional factor of 3 is used to account

for interspecies extrapolation. A full 10-fold adjustment for interspecies extrapolation is not deemed necessary due to the use of dosimetric adjustments. An uncertainty factor of 3 is applied for data base deficiencies because of the lack of certain information from the chronic exposure bioassay (e.g., urinalysis results, serum chemistry, and limited reporting of motor activity/clinical signs during exposure).

MF -- None

___I.B.4. ADDITIONAL STUDIES / COMMENTS (INHALATION RfC)

Information on human exposure to MTBE is limited. Humans are acutely exposed to MTBE as a part of a medical treatment to dissolve cholesterol gallstones (Thistle, 1992). Injection of the gall bladder with a high dose of MTBE can be associated with several types of health effects (e.g., nausea, vomiting, sleepiness). Minor transient mucosal damage in the gallbladder has been demonstrated with extensive exposure, but no clinically significant consequences have been reported. One patient has been reported to have developed intravascular hemolysis and renal failure following inadvertent extravasation of a large bolus of MTBE (Ponchon et al., 1988). Reliable data from epidemiology studies of human exposure to airborne MTBE are not currently available.

In a chronic inhalation study (Burleigh-Flayer et al., 1992), CD-1 mice (50 males, 50 females/group) were exposed to mean concentrations of 402, 3014, or 7973 ppm MTBE vapors (1442, 10,816, or 28,843 mg/cu.m) for 6 hours/day, 5 days/week (duration-adjusted values are 258, 1288, and 2575 mg/cu.m, respectively) for 18 months. The control animals breathed air. Hematology (all mice) and urinalysis (20 mice/sex) were performed halfway through the experiment (control and high-concentration groups) and prior to final sacrifice (all groups). In addition, corticosterone was measured on 10 mice/sex/group prior to sacrifice. Clinical signs, body weights, organ weights, and food consumption were monitored. A complete necropsy and histopathology, which included examination of the nasal turbinates and the lower respiratory tract, was performed on all animals.

Male mice from the high-exposure group exhibited an increased mortality rate, probably due to a slightly increased frequency of obstructive uropathy. However, the frequency of death due to this disease in the high-concentration group was still within the range noted for historical controls (Maita et al., 1988). Ataxia was observed in 50/50 animals (both sexes) exposed to the high MTBE concentration. In addition, prostration was noted between days 25 and 522 in 8/50 female mice exposed to the highest concentration (vs. 1/50 controls). Other effects reported in both sexes of the high-concentration group included decreased body weight gain and absolute body weight (not statistically significant for females), and a slight decrease in urinary pH. No concentration-related hematologic effects were reported.

Concentration-related increases in liver weight (absolute and relative to body and brain weights) were reported in both male and female mice. In the females, the liver weight increases were statistically significant at all but

the lowest exposure level ($p < 0.01$). In males, significant increases in liver weights were observed at the lowest exposure level ($p < 0.05$), but the only measure that indicated a concentration response was liver weight relative to brain weight ($p < 0.05$).

Absolute and relative male kidney weights were significantly increased in the lowest ($p < 0.01$) and mid-exposure groups ($p < 0.05$), but, as with the male liver weights, the increases were less than 10%, and a concentration-response relationship was not apparent (i.e., there was no statistical difference at the high-exposure level and significance at the mid-exposure level was less than at the low-exposure level). Female kidney weights were only increased significantly ($p < 0.01$) relative to body weight for animals exposed to the highest concentration.

Decreases in absolute brain weight were also reported in both sexes of the high-concentration group (6% for both sexes; $p < 0.01$). Absolute and relative spleen weights were increased for the high-exposure group females ($p < 0.01$), and absolute and relative adrenal weights were increased for the high-exposure group males ($p < 0.01$).

Histopathologic evaluation revealed no lesions in any organ except the liver. An increased incidence of hepatocellular hypertrophy was seen at the highest exposure level in both sexes, but was only significant ($p < 0.05$) in the male mice.

The increased liver, kidney, and adrenal weights, as well as the decreased brain weights, reported in this study at the highest exposure level are consistent with the subchronic rat study (Dodd and Kintigh, 1989). Although statistically significant ($p < 0.05$) increases in both absolute and relative liver and kidney weights were observed in the low- and mid-concentration groups, the male liver and kidney weights did not tend to increase with increasing exposure concentration, and the female liver and kidney weight increases (both absolute and relative) at the low- and mid-concentration levels were only 9% or less over controls. The high-exposure level is considered a LOAEL [LOAEL(HEC) = 2575 mg/cu.m] based on the significant increase in absolute (females only) and relative liver weights (around 30%; $p < 0.01$), the increased incidence of anesthetic effects, and the significant (as much as 24%) decrease in body weight. The decreased survival time in the male mice may suggest that the highest concentration exceeded the MTD, but it may also be due to increased frequency of a spontaneous obstructive uropathy common in this strain of male mice. The mid-exposure level is considered a NOAEL [NOAEL(HEC) = 1288 mg/cu.m] for this study.

In a subchronic inhalation study (Dodd and Kintigh, 1989), Fischer 344 rats (25/sex/group) were exposed to mean concentrations of 797, 3920, or 8043 ppm MTBE vapors (2873, 14,133, or 28,998 mg/cu.m) for 6 hours/day, 5 days/week (duration-adjusted values are 513, 2524, and 5178 mg/cu.m, respectively) for 13 weeks. The control animals breathed air. The high-exposure concentration was set at 50% of the LEL. Hematologic tests were performed before exposure (5/sex/group) and during weeks 5 and 14 (10/sex/group) of the study. Clinical observations were made of the groups; ophthalmic observations were made prior to the first exposure and at study end; and body weights, organ weights (15/sex/group), and food consumption were monitored. Ten rats/sex/group were

perfusion-fixed for microscopic evaluation of the nervous system tissues. Brain weights and measurements were taken on all perfusion-fixed rats, and light microscopic evaluations were performed on the nervous system of 6/sex/group. The remaining 15 rats/sex/group received complete necropsy evaluations. Nasal turbinates (four sections), trachea, and lung (three sections) were examined in the control and high-exposure groups and the lung only in the low- and mid-concentration groups. A battery of neurobehavioral tests was performed on 15 rats/sex/group prior to first exposure and at exposure weeks 1, 2, 4, 8, and 13, and motor activity was determined prior to first exposure and at exposure weeks 4, 8, and 13.

No treatment-related findings were noted for the respiratory tract. Lymphoid hyperplasia within the submandibular lymph nodes of the males in the high-exposure group was noted, but no reason was found for its occurrence.

Necropsy examination of nervous system tissue (10/sex/group) showed no evidence of treatment-related changes in exposed animals compared with the controls. However, at both the mid- and high-exposure levels, an absolute decrease in brain length was observed in male rats. Reductions in absolute brain weight in both sexes were noted at the high-exposure level, but not at the mid concentration. The authors observed no statistically significant changes in brain weight, expressed as a percentage of body weight, nor in brain width. Nevertheless, the effect on brain length was statistically significant ($p < 0.05$) and concentration related. Thus, this effect was felt to be consistent with the toxicity observed in other organ systems.

Dodd and Kintigh (1989) also evaluated the neurotoxic effects of MTBE using an FOB for 10 rats/sex/group and a motor activity test for the remaining 30 animals from each group. The mid- and high-concentration groups deviated from controls with respect to several FOB endpoints. The authors cite elevated body temperature in the high-exposure group males (day 7) and in the mid- and high-exposure group females (day 91). However, the overall downward trend in body temperature across control and exposure groups suggests an anomaly in the test procedure and calls to question the validity of these data. The authors note a decreased mean latency to rotate on the inclined screen in low- (days 14 and 28) and mid-concentration (days 7, 14, and 28) males. However, the data reported for this procedure are highly variable across groups and over time. Decreased hind limb grip strength was observed in mid-concentration males (days 28 and 91), but increased hind-limb grip strength was observed in mid-concentration females (day 91). Cumulative test-session motor activity was decreased for males exposed to the highest MTBE concentration (28% at day 55) and increased for females exposed to the lowest (20% at day 55) and mid concentrations (36% at day 55). The lack of a clearly defined concentration-response relationship calls into question the toxicological significance of these data.

Slight hematologic alterations were observed in both male and female rats exposed to mid- and high-exposure levels. All of these changes, however, were within the range of historical measurements for this species (Charles River Breeding Laboratories, 1984). The most noteworthy biochemical finding, however, was a significant ($p < 0.05$) increase in corticosterone levels for the high-exposure group, which is consistent with the observed increase of relative adrenal weight. The interaction of MTBE with the neuroendocrine

system (e.g., at the hypothalamus, pituitary, or adrenal glands) is unknown.

There were no exposure-related alterations in mean body weight for rats exposed to the low concentration. Male rats in the mid-concentration group had reduced body weight gain during the first week, but their mean body weights were similar to controls after week 5. Female rats in the mid-concentration group experienced a slight body weight gain reduction during weeks 3 and 4. Body weight gains were depressed in both male and female rats in the high-exposure group for the first 3 weeks of exposure. There was a concentration-related increase in liver, kidney, and adrenal weights relative to body weight of the treatment groups compared with controls. Absolute weights of these organs were also significantly increased, and relative weights were at least 10% greater ($p < 0.01$) than controls for male and female rats in the 4000- and 8000-ppm groups. In the mid- and high-exposure groups, relative weight increases in the males were 20 and 39% in the liver, 12 and 19% in kidneys, and 18 and 55% in adrenals, whereas increases in the females were 13 and 15% in the liver, 13 and 10% in kidneys, and 13 and 29% in adrenals, respectively. The relative lung weight in the high-concentration group was 3.5-6.5% greater than the controls. An increase in the degree, but not frequency, of hemosiderosis within the spleens of males exposed to the high concentration was observed, and there was also a mild increase in number and/or size of hyaline droplets within renal proximal tubules. Consistent with the chronic studies in rats (Chun et al., 1992) and mice (Burleigh-Flayer et al., 1992), the overall weight of evidence indicates that the mid-exposure level is moderately adverse to several organ systems, as indicated by decreased brain length and increased relative kidney (females), adrenal, and liver weights. Thus, a NOAEL of 797 ppm (2873 mg/cu.m) and a LOAEL of 3920 ppm (14,133 mg/cu.m) were determined.

CD-1 mice and Fischer 344 rats (5/sex/species/group) were exposed to 0, 2000, 4000, and 8000 ppm (0, 7211, 14,421, and 28,843 mg/cu.m) MTBE for 6 hours/day in the 13-consecutive-day, range-finding study (Dodd and Kintigh, 1989). Duration-adjusted exposure levels are 0, 1288, 2572, and 5150 mg/cu.m, respectively. Body weights, organ weights (brain, liver, kidneys, lungs, and adrenals), and individual clinical signs were monitored. Complete necropsy was performed on each animal, and all gross lesions were submitted to microscopy. Detailed behavioral observations were performed on rats only. A statistically significant depression in body weight gain was observed in male rats at the high-exposure concentration. There were no exposure-related effects on absolute body weight or body weight gain for mice. Relative liver weights (both sexes) and relative kidney weights (males only) were increased in rats at the high- and mid-exposure concentrations. Relative adrenal weights were increased at the high concentration in both sexes. Relative brain weights in the female rats in the 8000-ppm group were also significantly reduced. For mice, relative liver weights were increased at all concentrations (females only at the low- and mid-exposure levels). There were no weight changes in the lungs, brains, adrenals, or testes of mice when compared with control mean weights. No treatment-related macroscopic lesions were observed in either species. Reversible behavioral alterations (ataxia, decreased startle and pain reflexes, and decreased muscle tone) were observed in both sexes of rats exposed to 8000 ppm. These data suggested that 2000 ppm was a minimal effect level based on the relative liver weight changes in the female rats.

Greenough et al. (1980) exposed Sprague-Dawley rats (10/sex/group) to MTBE at 250, 500, or 1000 ppm (901, 1802, or 3605 mg/cu.m) 6 hours/day, 5 days/week for 13 weeks (duration-adjusted concentrations are 161, 322, or 644 mg/cu.m, respectively). Controls inhaled air only. Food and water consumption, body and organ weights, clinical signs, ophthalmoscopy, necropsy, and histopathology of animals were reported. Histopathology included examination of one transverse section through the nasal cavity, a series of transverse sections through the larynx and trachea, and one cut through the left lung (control and high-exposure groups) and cuts through both lungs (low- and mid-exposure groups).

No clinical signs were observed. Mean body weights were inconsistent, and differences were less than 10% compared with controls. The 1000-ppm females had significant ($p < 0.05$) reductions in absolute and relative (27% decrease) lung weights compared with controls. The 500- and 1000-ppm males showed a mean decrease of 8% in relative lung weight compared with controls. However, these findings do not appear to be concentration related, are not associated with adverse histopathologic or functional observations, and are not reproduced in the Dodd and Kintigh (1989) study. Significant ($p < 0.05$) differences in the absolute weights of the heart (male) and thymus (female) of 1000-ppm animals, kidneys of 500-ppm males, and adrenals of 250-ppm females were reported, but were not concentration-related changes. Histopathologic effects observed in the nasal cavity, larynx, trachea, and lungs of treated and control animals included focal inflammatory changes (pulmonary lymphoid vascular cuffing, localized polymorphonuclear leukocytes, and alveolar macrophages), epithelial and goblet cell hyperplasia, and congestion (lung only). Although these changes occurred in control and exposed animals, the changes did not appear to be concentration related and may be indicative of infection due to inadequate description of animal husbandry; any attempt to isolate causative organisms precludes conclusion. The possibility thus remains that respiratory effects of MTBE may have been unfounded by concomitant respiratory infection.

Hematologic and clinical chemistry tests were performed only on the control and 1000-ppm groups. Hemoglobin levels were increased ($p < 0.001$), as were BUN levels ($p < 0.05$) in 1000-ppm male rats compared with control values after 13 weeks of exposure. Female rats in the 1000-ppm group showed a significant decrease ($p < 0.05$) in LDH levels, as well as an increase in glucose and albumin levels. The mean corpuscular hemoglobin concentration (MCHC) increased significantly in 1000-ppm males ($p < 0.01$) and decreased in females ($p < 0.05$). It could not be determined if any changes were concentration related because the two low-concentration groups were not evaluated. These effects are not corroborated by the Dodd and Kintigh (1989) study at higher concentrations. A free-standing NOAEL of 1000 ppm [3600 mg/cu.m; NOAEL(HEC) = 3600 mg/cu.m] was determined for this study based on the lack of treatment-related effects in any organ or system.

Gill (1989) evaluated neurotoxicity of MTBE in a single acute inhalation study in which Fischer 344 rats (22/sex/group) were exposed to 0, 800, 4000, or 8000 ppm MTBE (0, 2884, 14,421, and 28,843 mg/cu.m) for 6 hours. Transient increases in motor activity were observed for males in the 800- and 4000-ppm exposure groups. After 1 hour of exposure, a significant ($p < 0.01$) increase

in the incidence of abnormal gait was observed in the 8000-ppm group. This was evidenced by a concentration-dependent increase in the incidence and severity of ataxia and duck-walk gait in males and females at the two highest concentrations. Labored respiratory pattern, increased lacrimation, decreased muscle tone, decreased mean performance on the treadmill, increased mean latency to tail withdrawal reflex, increased mean forelimb grip strength, and increased hindlimb splay were also observed in the 8000-ppm group ($p < 0.01$) at 1 hour of exposure. None of these motor function changes remained after 6 hours of exposure. Results also show that a 6-hour exposure to 8000 ppm MTBE significantly affected the motor activity of rats, especially during the first 50 minutes of the test session. The NOAEL based on these neurologic effects is 4000 ppm (14,421 mg/cu.m), and the LOAEL is 8000 ppm (28,843 mg/cu.m).

A 9-day inhalation study was performed (Bio/Dynamics, 1984) on Sprague-Dawley rats (20/sex/group) in which fasted and nonfasted animals were exposed to concentrations of 101, 300, 1020, and 2970 ppm MTBE vapors (364, 1082, 3677, and 10,708 mg/cu.m) 6 hours/day, 5 days/week. Lacrimation, conjunctival swelling, and corneal changes were observed in both treated and control animals; however, statistical significance was not reported. Although data were not shown, the authors report that there was a greater incidence of these clinical signs in males. A significant increase in the relative liver weight was evident in the fasted animals at 2970 ppm. Relative adrenal weights were significantly elevated in nonfasted, 300-ppm females and relative kidney weights were increased ($p < 0.05$) in nonfasted females exposed to 300 and 2970 ppm. Because a similar trend was not seen in fasted females at these exposure levels, and because these findings apparently were not concentration related, these observations in the nonfasted females are not considered treatment related. Both the nasal mucosa and the trachea were examined microscopically in controls and rats exposed to 1020 and 2970 ppm. Microscopic examinations revealed a significant increase in incidence of chronic inflammation in the nasal mucosa and the trachea at 1020 and 2970 ppm compared with pretest controls, but lung weight was not different from controls.

Savolainen et al. (1985) exposed 3-month-old male Wistar rats (20/group) to 50, 100, or 300 ppm MTBE vapor (181, 361, or 1082 mg/cu.m) 6 hours/day, 5 days/week for 2-15 weeks (duration-adjusted concentrations are 32, 64, or 193 mg/cu.m., respectively). Five animals from each chamber were weighed and sacrificed after weeks 2, 6, 10, and 15. The rats were bled, and their cerebral hemispheres, livers, kidneys, samples of right gluteal muscle (1 g), and samples of perirenal fat (1 g) were taken at autopsy. Although body weights did not differ significantly between groups early in the study, exposed rats did have higher weights than controls by week 15; mean weights were 365 g, 408 g (12% increase), 420 g (15% increase), and 407 g (12% increase) in animals exposed to 0, 50, 100, and 300 ppm, respectively. A significant ($p < 0.05$) concentration-dependent increase in microsomal uridine diphosphate-glucuronosyltransferase activity in liver and kidney, as well as NADPH cytochrome c-reductase activity in kidney, occurred after 2 weeks of exposure. These effects were not observed after 15 weeks of exposure. The study was limited because histopathology was not conducted and organs were not weighed.

Conaway et al. (1985) exposed pregnant Sprague-Dawley rats (23-25/group) and pregnant CD-1 mice (24-29/group) to 0, 260, 1100, or 3300 ppm MTBE (0,

937, 3965, or 11,897 mg/cu.m) 6 hours/day during gestational days 6-15. Maternal body weights were recorded for both species on days 0, 6, 12, 15, and 18 and on day 20 for rats. Physical examinations for signs of toxicity were performed at the same time as weights were recorded. Food and water consumption was recorded for days 6-9, 9-12, 12-15, and 15-18 and for days 18-20 for rats. Dams were sacrificed on day 20 (rats) or day 18 (mice) by carbon dioxide inhalation. Laparotomies were performed, and dams and pups were examined for gross abnormalities. Each fetus was weighed, and crown-rump distance was recorded. Late and early resorptions were scored. When no uterine implantation sites were observed, the uterus was stained to examine the foci of implantation. One-third of the fetuses in each litter were examined for soft-tissue abnormalities, and two-thirds of the fetuses were examined for skeletal abnormalities.

The pregnancy rate in rats was similar for all groups. Organ weights were not significantly different in exposed animals compared with control values. The mean number of corpora lutea, implantations, resorptions, and live fetuses was not significantly different among groups. Fetuses were weighed and examined for deformities, but no significant incidence of soft-tissue or skeletal anomalies was observed. A free-standing NOAEL of 3300 ppm [11,897 mg/cu.m; NOAEL(HEC) = 11,897 mg/cu.m] for reproductive and developmental toxicity effects was determined for rats with no reported maternal toxicity.

In mice, a slight increase in the incidence of lacrimation was observed among females (groups not specified) during exposure. The number of implantations in treatment groups was not statistically different compared with controls. The numbers of resorptions were 17, 11, and 17.3% in the 260-, 1100-, and 3300-ppm groups, respectively, compared with 9% in controls. These differences are of questionable significance because they do not appear to be concentration dependent, and the high number of resorptions in the low- and high-exposure groups were due to nearly complete resorptions in two females of the low-exposure group and complete resorption in two females of the high-exposure groups. Excluding the data for these four females, resorption data for these groups did not differ from controls. Mean fetal weights in treated animals were not significantly different from the controls. Soft-tissue anomalies per litter or per fetus were not found to be different among groups. Although not statistically significant, concentration-related skeletal variations per litter were found to be 2/27 (7.4%) in the control group and 3/26 (11.5%), 4/25 (16%), and 6/27 (22.2%) in the 260-, 1100-, and 3300-ppm groups, respectively. Cleft palates were noted in control (0.7%, 2/281), 260-ppm (0%, 0/265), 1100-ppm (0.4%, 1/251), and 3300-ppm (0.7%, 2/290) groups. A free-standing NOAEL of 3300 ppm [11,977 mg/cu.m; NOAEL(HEC) = 11,977 mg/cu.m] for developmental effects was determined for mice with minimal indications of maternal toxicity.

Pregnant CD-1 mice (30/group) were exposed to MTBE at concentrations of 0, 1035, 4076, and 8153 ppm (0, 3731, 14,695, and 29,394 mg/cu.m) 6 hours/day from gestational days 6 to 15 (Bushy Run Research Center, 1989a). No animals died and none aborted during the exposure period. Three dams at 0 ppm and two dams at 400 ppm delivered early and were removed from the study. The remaining dams were sacrificed on day 18 of gestation. No signs of maternal toxicity were observed in the dams exposed to 1035 ppm. At 4076 ppm, there were slight, but not statistically significant, indications of reduced

maternal body weight and body weight gain. Though the only observation for this exposure group reported was lacrimation in one dam, the authors indicate in the abstract and text of the report that hypoactivity and ataxia were observed in dams at 4076 and 8153 ppm. Clinical signs of maternal toxicity, including hypoactivity, ataxia, prostration, labored respiration, lacrimation, and periocular encrustation, were significantly increased at 8153 ppm. Significant reductions in food consumption, body weight, and body weight gain were also observed in dams exposed to 8153 ppm. A NOAEL of 1035 ppm [3731 mg/cu.m; NOAEL(HEC) = 3731 mg/cu.m] and a LOAEL of 4076 ppm [14,695 mg/cu.m; LOAEL(HEC) = 14,695 mg/cu.m] were determined for maternal toxicity.

MTBE did not affect the number of corpora lutea, total implants, or preimplantation loss per litter in any exposure group. There were significant ($p < 0.01$) increases in the number of nonviable implantations per litter, late resorptions, and dead fetuses; and significant reductions in the number of viable implantations ($p < 0.01$), percent of live fetuses ($p < 0.01$), and percent of male fetuses ($p < 0.05$) in the 8153-ppm group. Fetal body weight per litter (male and female) were significantly ($p < 0.01$) decreased at 4076 and 8153 ppm. A significant reduction in the incidence of partial fetal atelectasis and an increase in fetal atelectasis occurred at 8153 ppm. There were 24 skeletal variations (i.e., defects in cervical, thoracic, and caudal centra, forepaws, hindpaws, sternebrae, and skull plates/bones), all indicative of reduced ossification, that were significantly elevated in fetuses at 8153 ppm. There was a decreased incidence of unossified intermediate phalanges of the hindlimb at the high concentration. At 4076 ppm, there were seven skeletal variations related to reduced ossification (cervical centra, forepaw, hindpaw, and sternebrae) that showed a significantly increased incidence. At 1035 ppm, a significantly increased incidence of poorly ossified intermediate phalanges of the hindlimb was found. This finding was probably not treatment related because the alteration was not seen at the higher concentrations. In general, the effects were significant at the $p < 0.01$ level. A NOAEL of 1035 ppm [3725 mg/cu.m; NOAEL(HEC) = 3725 mg/cu.m] and a LOAEL of 4076 ppm (14,670 mg/cu.m) were determined for mice based on fetal body weight reductions with minimal maternal toxicity.

Developmental toxicity in rabbits was also investigated by Bushy Run Research Center (1989b). Pregnant New Zealand white rabbits (15/group) were exposed to 0, 1021, 4058, and 8021 ppm MTBE (0, 3681, 14,630, and 28,918 mg/cu.m) 6 hours/day, during gestational days 6-18. None of the does died, aborted, delivered early, or had to be removed from the study. There were no differences in maternal body weights among the groups. Reduced maternal body weight gain and food consumption were observed during the major period of organogenesis at 4058 and 8021 ppm. However, there were large standard deviations across the groups for body weight gain measurements. Relative liver weight was significantly increased by 14% ($p < 0.05$), and absolute liver weight was slightly, but not significantly, increased in does exposed to 8021 ppm. No histopathologic examination of the liver was conducted. The number of corpora lutea, resorptions, and viable and nonviable implantations were not significantly different among groups. Fetal body weights per litter were not statistically different among groups. There was no significant difference in the incidence of fetal malformations. This study identifies a free-standing NOAEL for developmental toxicity in rabbits of 8021 ppm [28,918 mg/cu.m; NOAEL(HEC) = 28,918 mg/cu.m].

Groups of male and female rats received a single 6-hour exposure to MTBE vapor in nose-only inhalation chambers at targeted MTBE concentrations of 400 and 8000 ppm and daily repeat 6-hour exposures for 15 days at a targeted MTBE concentration of 400 ppm (Ferdinandi et al., 1990). Four rats/sex/group were then euthanized and examined. Steady-state plasma concentrations were reached at approximately 4 to 6 hours for MTBE and roughly 6.5 hours for TBA, the principal metabolite of MTBE. MTBE-metabolizing enzymes were saturated during high-concentration exposure. The elimination half-life (t1/2) of MTBE was approximately the same after single low- and high-concentration exposures (0.52 and 0.63 hours, respectively). After the repeat exposures, the MTBE t1/2 was slightly shorter (0.48 and 0.51, respectively). The TBA t1/2 ranged from 2.8 to 3.4 hours after the low- and high-concentration single exposures. After the repeat exposure regimen, the TBA t1/2 was significantly lower (1.8 and 1.5 hours in the male and female rats, respectively). There was a slight, but statistically significant, sex difference in the pharmacokinetics of MTBE (e.g., plasma clearance was faster in females), but no sex differences in the elimination kinetics of TBA were observed.

___I.B.5. CONFIDENCE IN THE INHALATION RfC

Study -- Medium
Data Base -- Medium
RfC -- Medium

Confidence in the study is medium. It was well-designed (e.g., with respect to exposure protocol, number of animals, and exposure duration), identified a consistent LOAEL and NOAEL for a constellation of organ systems, and involved extensive histopathology on both sexes. However, the results of the rat study are confounded by the high mortality in the males, which is presumed to be the result of rat chronic nephropathy. Further, the lack of certain information from the chronic bioassay reduces confidence in the study (e.g., urinalysis results, serum chemistry, and limited reporting of motor activity/clinical signs during exposure). Confidence in the data base is medium to high because of the existence of chronic and subchronic bioassays in more than one species, developmental studies in several different species, and the existence of single- and two-generation reproductive studies in the rat. Medium to high confidence in the RfC follows.

___I.B.6. EPA DOCUMENTATION AND REVIEW OF THE INHALATION RfC

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- U.S. EPA, 1989, 1993

Agency Work Group Review -- 06/13/91, 04/01/93, 07/21/93

Verification Date -- 07/21/93

___I.B.7. EPA CONTACTS (INHALATION RfC)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX) or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Methyl tert-butyl ether (MTBE)
CASRN -- 1634-04-4

Not available at this time.

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_VI. BIBLIOGRAPHY

Substance Name -- Methyl tert-butyl ether (MTBE)
CASRN -- 1634-04-4
Last Revised -- 09/01/93

__VI.A. ORAL RfD REFERENCES

None

__VI.B. INHALATION RfD REFERENCES

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__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

None

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_VII. REVISION HISTORY

Substance Name -- Methyl tert-butyl ether (MTBE)
CASRN -- 1634-04-4

Date	Section	Description
08/01/91	I.B.	Inhalation RfC now under review
12/01/91	I.B.	Inhalation RfC on-line
12/01/91	VI.	Bibliography on-line
03/01/93	I.A.	Oral RfD now under review
05/01/93	I.B.	Inhalation RfC noted as pending change
05/01/93	I.B.6.	Work group review date added
08/01/93	I.B.	Withdrawn; new RfC verified (in preparation)
08/01/93	I.B.6.	Work group review date added

08/01/93 I.B.7. EPA contact changed
08/01/93 VI. Bibliography withdrawn
09/01/93 I.B. Inhalation RfC replaced; RfC changed
09/01/93 VI.B. Inhalation RfC references on-line

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SYNONYMS

Substance Name -- Methyl tert-butyl ether (MTBE)
CASRN -- 1634-04-4
Last Revised -- 12/01/91

1634-04-4
Propane, 2-methoxy-2-methyl-
methyl tert-butyl ether
T-BUTYL METHYL ETHER
Ether methyl tert-butylique [French]
Ether, tert-butyl methyl
HSDB 5847
METHYL 1,1-DIMETHYLETHYL ETHER
METHYL-tert-BUTYL ETHER
Methyl-tert-butylether
Metil-terc-butileter [Spanish]
tert-Butyl methyl ether
2-METHOXY-2-METHYLPROPANE
2-METHYL-2-METHOXYPROPANE

Methyl-tert-butyl ether; Downloaded 8/13/97

Methyl-tert-butyl ether; Downloaded 8/13/97

0436
Naphthalene; CASRN 91-20-3 (04/01/97)

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Naphthalene

File On-Line 12/01/90

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	09/01/94
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	08/01/95

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Naphthalene
CASRN -- 91-20-3

Not available at this time.

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Naphthalene
CASRN -- 91-20-3

Not available at this time.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Naphthalene
CASRN -- 91-20-3
Last Revised -- 08/01/95

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

NOTE: NOTE ADDED IN JULY 1995: Subsequent to the verification of this cancer assessment in 1990, the National Toxicology Program completed a two-year cancer bioassay (1991); its results suggest that naphthalene may be more appropriately classified as a possible human carcinogen (Group C under current EPA guidelines). The NTP concluded, "Under the conditions of these 2-year studies, there was no evidence of carcinogenic activity of naphthalene in male B6C3F1 mice exposed by inhalation to concentrations of 10 or 30 ppm for 6 hours daily, 5 days per week, for 103 weeks. There was some evidence of carcinogenic activity of naphthalene in female B6C3F1 mice, as indicated by the increased incidences of pulmonary alveolar/bronchiolar adenomas."

The following summary was written in December 1990:

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to human carcinogenicity

Basis -- Based on no human data and inadequate data from animal bioassays.

___II.A.2. HUMAN CARCINOGENICITY DATA

None.

___II.A.3. ANIMAL CARCINOGENICITY DATA

Inadequate. The National Toxicology Program is currently evaluating naphthalene for carcinogenicity in mice by the inhalation route; final results are not yet available (SEE NOTE ADDED IN JULY 1995).

A group of 28 rats (in-house strains BDI and BDIII) was exposed to a diet supplemented with naphthalene, 6 times/week (Schmahl, 1955). Treatment was stopped when total dose was 10 g/rat. The average daily dose was approximately 10 to 20 mg/day (approximately 30 to 60 mg/kg/day). Tumors were evaluated in animals that died spontaneously at about 700 to 800 days of age. No carcinogenic responses were reported.

In a short-term pulmonary tumor bioassay, Adkins et al. (1986) exposed groups of 30 female A/J strain mice by inhalation to 0, 10, or 30 ppm naphthalene for 6 hours/day, 5 days/week for 6 months. While naphthalene caused a statistically significant increase in the number of adenomas per mouse lung, there was no apparent dose-response. This assay is considered to be a short-term, in vivo, lung tumor assay.

Tsuda et al. (1980) administered a single gavage dose of 100 mg/kg naphthalene in corn oil to a group of 10 F344 rats (sex not specified) at 12 hours after partial hepatectomy. A vehicle control group of 10 rats was included. At 2 weeks after surgery, 2-acetylaminofluorene was added to the diet at 200 ppm to inhibit proliferation of "nonresistant" hepatocytes. After 1 week of dietary 2-acetylaminofluorene, a single 2.0 mL/kg dose of carbon tetrachloride was given to necrotize "nonresistant" hepatocytes and permit proliferation of "resistant" hepatocytes. Feeding of 2-acetylaminofluorene continued for 1 week, followed by a basal diet for 1 week. The rats were then sacrificed and livers were sectioned and histochemically examined for the number and size of gamma-glutamyl transpeptidase (GGT) positive foci. These foci contain cells that are "resistant" to the necrotizing effects of carbon tetrachloride and to the proliferation-inhibiting effects of 2-acetylaminofluorene and are considered to represent an early stage in the process of neoplastic transformation. Neither the number nor the size of GGT foci appeared to be increased in naphthalene-treated rats compared with vehicle controls.

A group of 10 rats (in-house strains BDI and BDIII) received intraperitoneal injections of naphthalene (20 mg/rat) once a week for 40 weeks (Schmahl, 1955). Another group of 10 rats served as a control group. Animals were evaluated after spontaneous death. No carcinogenic responses were reported.

Coal tar-derived naphthalene that contained approximately 10% unidentified impurities was administered to 40 white rats (sex unspecified) by seven subcutaneous injections of 500 mg/kg naphthalene in sesame oil at 2-week intervals. Lymphosarcomas were found in 5/34 surviving rats at 18 months (14.7%), whereas vehicle controls had a 2% incidence of these tumors. This study is of limited value because of the presence of potentially carcinogenic impurities in the naphthalene and because prior to injection carbofuchsin was applied dermally to the injection site (Knake, 1956).

Inbred black mice (25/group) were painted with 0.5% coal tar-derived naphthalene (10% unidentified impurities) in benzene 5 days/week for life. Four treated mice develoed leukemias in contrast to 0/21 vehicle controls; the untreated control incidence was 0.4%. The value of this study for assessing carcinogenicity is very limited due to the presence of potentially carcinogenic impurities. Moreover, the vehicle in the study has been shown to cause leukemias (Knake, 1956). Other mouse skin-painting tests of naphthalene as a complete carcinogen and as an initiator of carcinogenicity were negative or inconclusive (Kennaway, 1930; Schmeltz et al., 1978).

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

With one exception naphthalene was not positive when tested in a variety of genotoxicity assays. In reverse mutation assays using Salmonella typhimurium strains TA97, TA98, TA100, TA1535, TA1537, TA1538, UTH8413 and UTH8414, naphthalene at concentrations of up to 2.5 mg/plate was not positive either with or without hepatic homogenates (McCann et al., 1975; Anderson and Styles, 1978; Florin et al., 1980; Gatehouse, 1980; Connor et al., 1985; Ho et al., 1981; Sakai et al., 1985; Mortelmans et al., 1986; Bos et al., 1988). Narbonne et al. (1987) reported that in the presence of hepatic homogenates naphthalene at 5 and 10 ug/plate was mutagenic for S. typhimurium TA1538; however, naphthalene was not positive at concentrations of 50, 100 and 1000 ug/plate. There was no increase in forward mutation frequency for Salmonella. At concentrations of up to 1.6 mM, naphthalene was not positive in S. typhimurium forward mutation assays (Kaden et al. 1979; Seixas et al., 1982). In a DNA damage assay using S. typhimurium TA1535 Nakamura et al. (1987) reported that naphthalene at concentrations of up to 83 ug/mL was not positive. In phage induction assays using Escherichia coli as a host, naphthalene at concentrations of up to 2 mg/mL did not yield positive results (Ho and Ho, 1981; Mamber et al. 1984). DNA damage assays with naphthalene were not positive in E. coli (Mamber et al., 1983) or in primary rat hepatocyte cultures (Sina et al., 1983). Transformation assays in Swiss mouse embryo cells (Rhim et al., 1974) and in rat embryo cells (Freeman et al., 1973) were not positive.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

None.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

None.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

Source Document -- U.S. EPA, 1986, 1990

The 1990 Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons has undergone Agency and external review.

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Work Group Review -- 02/07/90, 08/05/92, 04/06/95

Verification Date -- 02/07/90

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX) or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

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_VI. BIBLIOGRAPHY

Substance Name -- Naphthalene
CASRN -- 91-20-3
Last Revised -- 12/01/90

__VI.A. ORAL RfD REFERENCES

None

__VI.B. INHALATION RfC REFERENCES

None

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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_VII. REVISION HISTORY

Substance Name -- Naphthalene
CASRN -- 91-20-3

Date	Section	Description
12/01/90	II.	Carcinogen assessment on-line
12/01/90	VI.	Bibliography on-line
01/01/92	IV.	Regulatory Action section on-line
09/01/92	II.	Classification noted as pending change
09/01/92	II.D.2.	Work group review date added
11/01/93	I.A.	Work group review date added
09/01/94	I.A.	Work group review date added

05/01/95 II. Pending change note replaced
05/01/95 II.D.2. Work group review date added
07/01/95 II. Pending change note replaced; see new note
08/01/95 II. Note revised
08/01/95 II.A.3. Paragraph 1 revised

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SYNONYMS

Substance Name -- Naphthalene
CASRN -- 91-20-3
Last Revised -- 12/01/90

91-20-3
Naphthalene
Albocarbon
Caswell No. 587
Dezodorator
EPA Pesticide Chemical Code 055801
HSDB 184
MOTH BALLS
MOTH FLAKES
Naftalen [Polish]
Naftaleno [Spanish]
Naphtalene [French]
Naphthalene
Naphthalin
Naphthaline
Naphthene
NAPTHALENE, molten
NCI-C52904
NSC 37565
RCRA WASTE NUMBER U165
TAR CAMPHOR
UN 1334
UN 2304
WHITE TAR

Napthalene; Downloaded 8/13/97

Napthalene; Downloaded 8/13/97

0486
n-Hexane; CASRN 110-54-3 (04/01/97)

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR n-Hexane

File On-Line 07/01/90

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	
Inhalation RfC Assessment (I.B.)	on-line	07/01/93
Carcinogenicity Assessment (II.)	no data	09/01/91

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- n-Hexane
CASRN -- 110-54-3

Not available at this time.

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- n-Hexane
CASRN -- 110-54-3

Last Revised -- 07/01/93

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

___I.B.1. INHALATION RfC SUMMARY

Critical Effect	Exposures*	UF	MF	RfC
Neurotoxicity; electrophysiological alterations Epidemiological Inhalation Study Sanagi et al., 1980	NOAEL: None LOAEL: 204 mg/cu.m. (58 ppm) LOAEL[ADJ]: 73 mg/cu.m LOAEL(HEC): 73 mg/cu.m	300	1	2E-1 mg/cu.m
Epithelial lesions in the nasal cavity 90-Day Mouse Inhalation Study Dunnick et al., 1989	NOAEL: 1762 mg/cu.m (500 ppm) NOAEL(ADJ): 315 mg/cu.m NOAEL(HEC): 38 mg/cu.m LOAEL: 3525 mg/cu.m (1000 ppm) LOAEL(ADJ): 629 mg/cu.m LOAEL(HEC): 77 mg/cu.m			

*Conversion Factors: MW = 86.18.
Sanagi et al., 1980: Assuming 25C and 760 mmHg, LOAEL (mg/cu.m.) = 58 ppm x 86.18/24.45 = 204. This is an extrarespiratory effect of a soluble vapor. The LOAEL is based on an 8-hour TWA occupational exposure. MVho = 10 cu.m/day, MVh = 20 cu.m/day. LOAEL(ADJ) = 204 mg/cu.m x (MVho/MVh) x 5 days/7 days = 73 mg/cu.m.

Dunnick et al., 1989: Assuming 25C and 760 mmHg, NOAEL (mg/cu.m) = 500 ppm

x 86.18/24.45 = 1762. The NOAEL(HEC) was calculated for a gas:respiratory effect in the ET region. MVa = 0.04 cu.m/day, MVh = 20 cu.m/day, Sa(ET) = 2.9 sq. cm., Sh(ET) = 177 sq. cm. RGDR(ET) = (MVa/Sa) / (MVh/Sh) = 0.122. NOAEL(HEC) - NOAEL(ADJ) x RGDR = 315 mg/cu.m x 0.122 - 38 mg/cu.m. LOAEL(HEC) = LOAEL(ADJ) x RGDR = 629 mg/cu.m x 0.122 = 77 mg/cu.m.

___I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

Sanagi, S., Y. Seki, K. Sugimoto and M. Hirata. 1980. Peripheral nervous system functions of workers exposed to n-hexane at a low level. Int. Arch. Occup. Environ. Health. 47: 69-79.

Dunnick, J.K., D.G. Graham, R.S. Yang, S.B. Haber and H.R. Brown. 1989. Thirteen-week toxicity study of n-hexane in B6C3F1 mice after inhalation exposure. Toxicology. 57(2):163-172.

Sanagi et al. (1980) and Dunnick et al. (1989) have been chosen as co-critical studies in establishing the RfC for n-hexane. A principal reason for this is that a NOAEL cannot be derived from the Sanagi study which identifies only a free standing LOAEL. The Dunnick study identifies a LOAEL very similar to that in the Sanagi study in addition to identifying a NOAEL both of which are based on mild inflammatory lesions of the nasal epithelium. The RfC for n-hexane was based on the Sanagi study as there is considerable and compelling evidence that hexane is neurotoxic to humans.

Sanagi et al. (1980) conducted an epidemiology study on two age-matched groups consisting of 14 control workers and 14 exposed workers employed in a factory producing tungsten carbide alloys. The groups were matched with respect to age, stature, weight, alcohol consumption and smoking habits. Exposure was estimated with 22 personal samples taken from the breathing zones over a period of 2 years and reported on an 8-hour TWA exposure to solvent vapors consisting of n-hexane at 58 +/- 41 ppm (duration-adjusted = 73 mg/cu.m) and acetone at 39 +/- 30 ppm; no other solvent vapors were detected. Noticeably absent was methyl ethyl ketone as this chemical may apparently potentiate the neurotoxicity of n-hexane (Altenkirch et al., 1982; Veronesi et al., 1984). The exposure duration ranged from 1 to 12 years with an average of 6.2 years. Both groups underwent clinical neurological examinations (one examiner, blind design) with reference to cranial nerves, motor and sensory systems, reflexes, co-ordination, and gait. Neurophysiological studies performed included electromyography on muscles of the forearm and leg. Nerve stimulation studies (NSS) were performed with a surface electrode and included a number of parameters. Recordings were made in a temperature-controlled room allowing subjects 30 minutes to acclimate before the examinations. Skin temperatures were taken at several points along the nerve trunks with a thermocouple; there were no significant differences in average skin temperatures between these two groups. No neurological abnormalities were noted. However, neurophysiological tests showed that the mean motor nerve conduction velocities (MMCV) of the exposed group was significantly decreased over the values for the control group. Also, the residual latency (RL) of motor nerve conduction of the posterior tibial nerve in the exposed group was significantly slowed when compared with the nonexposed group. The

alterations observed are consistent with n-hexane-induced peripheral neuropathy observed in other studies in humans (Chang, 1987; Chang and Yip, 1987) and in animals (Schaumburg and Spencer, 1976; Miyagaki, 1967; Huang et al., 1989). Thus, this study supports the designation of 58 ppm (73 mg/cu.m) as a LOAEL.

Inhalation of n-hexane results in morphologic alterations in the respiratory tract in mice (Dunnick et al., 1989). A subchronic inhalation study with n-hexane (99%) was conducted in B6C3F1 mice (10/sex/dose) to evaluate and compare histopathologic nerve damage with neurologic damage determined by a series of behavioral tests. Exposure concentrations of 0, 500, 1000, 4000, or 10,000 ppm (0, 1762, 3525, 14,099, or 35,247 mg/cu.m, respectively) were administered 6 hours/day, 5 days/week (duration-adjusted = 0, 315, 629, 2518, or 6294 mg/cu.m). An additional group of animals was exposed to 1000 ppm (3525 mg/cu.m) for 22 hours/day, 5 days/week for 13 weeks (duration-adjusted = 2308 mg/cu.m) and was designated as the 1000 C group. Concentrations in each exposure chamber were monitored hourly by IR spectrophotometry; chamber concentrations were found to be within 15% of targeted concentrations. Clinical signs, body and organ weight, gross and histopathology, neuropathology and neurobehavioral tests were performed to assess toxicity. Organs examined included liver, spleen, kidneys, testis, uterus, trachea, lungs, bronchi, and the nasal cavity with nasal turbinates. Exposure had no effect on survival; 10 to 17% depression of final body weight relative to control weight was observed in males of the 1000 C group and in the high-dose males. Histopathologic changes included mild inflammatory, erosive, and regenerative lesions in the olfactory and respiratory epithelium of the nasal cavity in mice exposed to 1000 ppm (2308 mg/cu.m; group C), and higher concentrations; minimal lesions were observed in the 500-ppm (315 mg/cu.m) and 1000-ppm (629 mg/cu.m) exposure groups. An unequivocal relationship exists between the dose and the incidence and severity of these morphological alterations in female mice. Neurohistopathology showed modest paranodal axonal swellings in the tibial nerve in 6/8 mice of the 1000 C group (2308 mg/cu.m) and in 6/8 of the group exposed to 10,000 ppm (6294 mg/cu.m); the swellings were absent in the 8 control animals examined. The animals exposed to 500 ppm (315 mg/cu.m) and 1000 ppm for 6 hours/day (629 mg/cu.m) were not examined for neuropathological alterations. This study identifies a NOAEL of 500 ppm based on mild lesions of the nasal turbinates. The NOAEL(HEC) was calculated for a gas:respiratory effect in the ExtraThoracic (ET) ET region. MVa = 0.04 cu.m/day, MVh = 20 cu.m./day, Sa = (ET) 2.9 sq. cm., Sh = (ET) 177 sq. cm. RGDR = (MVa/Sa)/ (MVh/Sh) = 0.122. NOAEL(HEC) = NOAEL(ADJ) x RGDR = 315 mg/cu.m x 0.122 = 38 mg/cu.m. LOAEL(HEC) = LOAEL(ADJ) x RGDR = 629 mg/cu.m x 0.122 = 77 mg/cu.m.

The interpretation of results from this study is limited for a number of reasons. Neuropathological examinations were conducted only in the 1000 C group (2308 mg/cu.m), the 10,000-ppm group (6294 mg/cu.m) and the controls, not in the groups designated as representing the LOAEL or NOAEL. According to the severity grading of lesions provided in the paper, the average grade of the lesions seen at the LOAEL were "minimal to slight." The average grade of the lesions even at the highest exposure level ranged only from 1.2 to 3.0 (from "minimal to moderate"). Also, there was no dose-relationship in severity or incidence of pathologies in the nasal turbinates in the rats of the IRDC (1981) or Cavender et al. (1984) studies although the exposure levels

in these studies were much higher than those used in Dunnick et al. (1989).

___I.B.3. UNCERTAINTY AND MODIFYING FACTORS (INHALATION RfC)

UF -- The uncertainty factor of 300 reflects a factor of 10 to protect unusually sensitive individuals and 10 for the use of a LOAEL rather than a NOAEL. An additional factor of 3 is proposed for both the lack of data on reproductive and chronic respiratory effects.

MF -- None

___I.B.4. ADDITIONAL COMMENTS / STUDIES (INHALATION RfC)

In humans, sensorimotor polyneuropathy is the principal neurologic manifestation in long-term exposure to n-hexane, although cranial neuropathies, blurred vision, and abnormal color vision associated with macular changes have also been reported (Sobue et al., 1978; Yamamura, 1969; Paulson and Waylonis, 1976; Wang et al., 1986; Seppalainen et al., 1979).

In the studies reporting solvent-related neuropathies in workers, the exposure is only generally characterized, often with 500 ppm (duration-adjusted = 630 mg/cu.m) the lowest concentration cited. The study by Yamada (1967) reported polyneuropathy (with subsequent development of muscular atrophy and paresthesia in the distal extremities) in 17 workers exposed to concentrations of n-hexane varying between 500 ppm (630 mg/cu.m) and 1000 ppm (1260 mg/cu.m) in a pharmaceutical plant. An outbreak of polyneuropathy among 93 of the 1662 (5.6%) workers of a Japanese sandal manufacturing plant was reported by several researchers (Yamamura, 1969; Inoue et al., 1970; Iida, 1982; Sobue et al., 1978). In 88% of these 93 workers, numbness of the distal portion of the extremities was the first symptom observed. The etiologic agent was presumed to be hexane, which was used as a glue solvent; air concentrations of the commercial hexane (60 to 70% n-hexane) in the poorly ventilated pasting rooms ranged from 500 to 2500 ppm (duration-adjusted to 8-hour work day = 630 to 3147 mg/cu.m). Some workers were in these work areas for up to 14 hours/day. Abnormal electromyography and decreased conduction velocity were observed in 31 of the 44 cases (70%) examined for these parameters. Neuropathology revealed the characteristic alterations of n-hexane-induced neuropathy - giant axonal degeneration, and paranodal and internodal swellings of axons. In severe cases, the clinical manifestations progressed for about 2 months even after removal from the noxious environment. Because of the limitations of these studies concerning accurate exposure estimates, possible exposure by other routes, co-exposure to other solvents (see Altenkirch et al., 1982), improper industrial hygiene practices, and lack of control populations, a LOAEL in humans of 500 ppm (630 mg/cu.m) cannot be adequately justified based on any of these studies.

The following inhalation studies in animals provide effect levels of n-hexane toxicity with indicators of peripheral neuropathies as the critical effect. Thus, the NOAEL(HEC)s calculated for these studies were calculated

for a gas:extrarespiratory effect assuming periodicity was attained. Since the b:a lambda values are unknown for the experimental animals (a) and humans (h), a default value of 1.0 is used for this ratio. NOAEL(HEC) mg/cu.m = NOAEL(ADJ) x [b:a lambda(a) / b:a lambda(h)]. Study consideration is by increasing NOAEL(HEC) values.

Miyagaki (1967) continuously exposed groups (10/group) of male mice (SM-A strain) to 0, 100, 250, 500, 1000, or 2000 ppm commercial grade hexane (65 to 70% n-hexane; 0, 353, 881, 1762, 3525, or 7050 mg/cu.m) the remaining hydrocarbons were described as other hexane isomers), 6 days/week for 1 year (duration-adjusted = 0, 302, 755, 1510, 3020, or 6040 mg/cu.m). The following parameters were measured at the end of the study period: electromyography, strength-duration curves, electrical reaction time, and flexor/extensor chronaxy ratio. Also gait posture was noted and the grade of muscular atrophy estimated. Electromyographic analysis showed increased complexity of NMU (neuromuscular unit) voltages in 0/6 controls, 1/6 animals in the 100-ppm group, 3/6 animals examined in the 250-ppm group, 5/6 animals examined in the 500-ppm group, 3/3 animals examined in the 1000-ppm group, and 4/4 animals examined in the 2000-ppm group. Electromyography showed a similar dose-related increase both in incidence and severity of reduced interference voltages from muscles in animals exposed to 250 ppm and higher, but not in the controls (0/6 examined) nor in the 100-ppm group (0/6). A dose-related increase in abnormalities of strength-duration curves was also noted; slight fibrillation was detected in the electromyograms of 0/6 mice in the 100-ppm exposure group, 2/6 mice examined in the 250-ppm exposure group and in 0/6 in the 500-ppm group, whereas severe fibrillation was noted in 3/3 animals examined in the 1000- ppm group and in 4/4 examined in the 2000-ppm group. Presumably because of the hexane-induced neuropathies in evidence from the electromyographic analysis, abnormal posture and muscle atrophy were noted in a dose-related manner in animals exposed to concentrations of n-hexane at 250 ppm and higher (in the highest exposure group, where there was an unexplained assumption of normal posture in 3/4 animals examined). This study indicated that a neurotoxicity threshold between 100 and 250 ppm existed in mice, as neurotoxic effects were observed in mice exposed to 250 ppm and higher. Thus, this study identifies a NOAEL of 100 ppm (302 mg/cu.m) for neurotoxicity; when adjusted for 70% n-hexane the NOAEL becomes 0.7 x 302 mg/cu.m = 211 mg/cu.m. NOAEL(HEC) = 211 mg/cu.m.

This study is limited as the data from only 3 to 6 of the 10 animals was presented and the exposure was to unpure n-hexane. However, it should be noted that the exposure regimen in this study was the most protracted (1 year), with the animals exposed almost continuously (6 of 7 days, 24 hours/day), and that toxicity was seen in a dose-related fashion. In regard to the purity of the n-hexane, it is fairly certain that the main neurotoxic component of hexanes mixtures is n-hexane. The other common isomers present in n-hexane are apparently not neurotoxic as they can not form the neurotoxic metabolite hexane-2,5-dione (Ono et al., 1981; Lapadula et al., 1986).

Groups of Sprague-Dawley rats (12/sex/dose) were administered n-hexane vapor (purity not stated; obtained from J.T. Baker Chemicals) at concentrations of 0, 6, 26, or 129 ppm (0, 21, 92, or 455 mg/cu.m) for 6 hours/day, 5 days/week (duration-adjusted = 0, 3.8, 16.4, or 81 mg/cu.m) and at 0, 5, 27, or 126 ppm (0, 18, 95, or 444 mg/cu.m) for 21 hours/day, 7

days/week (duration-adjusted = 0, 15.4, 83, or 389 mg/cu.m). Both exposure regimens lasted 26 weeks (Bio/Dynamics, 1978). Neuropathology and neurological evaluations were performed, and hematology and clinical chemistry parameters were evaluated at 3 and 6 months. The study states that sections of the liver, lungs, kidneys, heart, and brain (apparently no tissue from the upper airways) were preserved, although no histopathology for these organs is discussed. The summary of the neuropathological study states that not a single animal exhibited the characteristic pathological signs of nervous system degeneration produced by n-hexane (paranodal thickening of peripheral nerves accompanied by giant axonal swellings in the CNS). This condition concurs with the observations of Altenkirch et al. (1982) for discrimination between age-related neuronal changes and alterations caused by n-hexane. While it can be deduced from the study that there were no animals with characteristic alterations at both peripheral and central sites, the association of any animal within a specific dose group was not possible due to lack of a proper key. From these results, the authors conclude that n-hexane does not elicit toxicity at the concentrations tested. Thus, the highest dose tested at the longest duration, 389 mg/cu.m, appears to be a no-effect level for neurotoxicity in this study. NOAEL(HEC) = 389 mg/cu.m.

Groups of male Sprague-Dawley-derived Charles River rats (14/group) were exposed to n-hexane plus mixed hexanes 22 hours/day, 7 days/week for approximately 6 months (IRDC, 1981). The concentrations were as follows: 0, 126 ppm n-hexane (444 mg/cu.m, duration-adjusted = 407 mg/cu.m), 125 ppm n-hexane + 125 ppm mixed hexanes, 125 ppm n-hexane + 375 ppm mixed hexanes, 125 ppm n-hexane + 1375 ppm mixed hexanes, and 502 ppm n-hexane (1769 mg/cu.m, duration-adjusted = 1622 mg/cu.m). Microscopic examination of the lungs, liver, kidneys, brain, gonads, spleen, peripheral nerves, gastrocnemius, and nasal turbinateswas performed on all animals. Neurotoxicity was observed in rats exposed to 502 ppm (1622 mg/cu.m) n-hexane. The most significant observations were abnormal gait in 5 of the 14 animals (apparently a consequence of muscle atrophy), axonal degeneration, and myelin vacuolization in 9 of 10 animals examined. The authors concluded that neurotoxicity appeared to be a specific response of n-hexane exposure, as no other treatment groups developed neuropathic/myopathic alterations. Changes in the livers of some animals were considered necrotic although the incidence was not dose related (3/10 examined in the 126-ppm group and 3/10 examined in the 502-ppm group). There was no dose-related increase in severity or incidence of pathologies in the nasal turbinates. Alterations in average values for both absolute and relative organ weights were noted for the liver and kidney in the animals exposed to 125 ppm n-hexane + 1375 ppm mixed hexanes and in the liver for the animals exposed to 502 ppm n-hexane. This study identifies a NOAEL of 125 ppm (407 mg/cu.m). NOAEL(HEC) = 407 mg/cu.m for axonal degeneration.

Huang et al. (1989) exposed Wistar male rats (8/dose) to n-hexane vapor (>99% pure) at 0, 500, 1200, or 3000 ppm (0, 1762, 4230, 10574 mg/cu.m) 12 hours/day, 7 days/week for 16 weeks (duration-adjusted = 0, 881, 2115, or 5287 mg/cu.m) and demonstrated a dose-dependent peripheral neurotoxicity induced by n-hexane exposure. The body weight gain and motor-nerve conduction velocity (MCV) in exposure groups show progressively concentration-dependent decreases compared to control values. The body weight was significantly depressed in the two highest exposure groups, but only slightly in the 500-ppm group. At of 1200 ppm and 3000 ppm n-hexane, MCV was significantly reduced.

Histopathologic examination revealed degeneration of peripheral nerves characterized by paranodal swellings and demyelination and remyelination in the myelinated nerve fibers in the two highest exposure groups which was more advanced in the highest exposure group. This study identifies a NOAEL(HEC) = 881 mg/cu.m.

Frontali et al. (1981) exposed Sprague-Dawley male rats (6-9/group) to 0, 500, 1500 or 5000 ppm (0, 1762, 5286, or 17,624 mg/cu.m; duration- adjusted = 0, 472, 1416, or 4721 mg/cu.m) of 99% n-hexane 9 hours/day, 5 days/week or to 2500 ppm (8812 mg/cu.m; duration-adjusted = 3147 mg/cu.m) 99% n-hexane 10 hours/day, 6 days/week for 14 to 30 weeks. A significant decrease in weight gain was observed in rats treated with 5000 ppm and 500 ppm of n-hexane. Pathological alterations characterized by giant axonal degeneration, and paranodal and internodal swellings of axons were observed in rats treated intermittently with 2500 ppm (after 30 weeks) and 5000 ppm n-hexane (after 14 weeks). This study identifies a NOAEL(HEC) of 1416 mg/cu.m for pathological alterations of the peripheral nerves.

A 13-week inhalation study was conducted in Fischer rats (5/sex/dose) (Cavender et al., 1984) in which concentrations of 0, 3000, 6500, or 10,000 ppm of >99.5% pure n-hexane vapors (0, 10,575, 22,911, or 35,247 mg/cu.m) were administered 6 hours/day, 5 days/week (duration-adjusted = 0, 1888, 4091, or 6294 mg/cu.m). No significant differences were observed in female body weights or in clinical observations, food consumption, ophthalmologic examination, neurological function, or hematological or serum chemistry parameters for either sex. Other than axonopathies no histopathological results are discussed although the study states that representative specimens of all organs (including the nasal cavity with associated structures) were processed for examination. This study identifies a NOAEL(ADJ) of 1888 mg/cu.m. NOAEL(HEC) = 1888 mg/cu.m.

Groups of male Wistar rats (Hannover strain; 5/group) were exposed under the following conditions: filtered air, 500 ppm n-hexane (1762 mg/cu.m; duration-adjusted = 1616 mg/cu.m), 700 ppm n-hexane (2467 mg/cu.m; duration-adjusted = 2262 mg/cu.m), 300 ppm n-hexane + 200 ppm methyl ethyl ketone (MEK), 400 ppm n-hexane + 100 ppm MEK, or 500 ppm n-hexane + 200 ppm MEK 22 hours/day, 7 days/week for a total of 9 weeks (Altenkirch et al., 1982). Two other groups were exposed to 700 ppm n-hexane (2467 mg/cu.m) or 500 ppm n-hexane + 200 ppm MEK for 8 hours/day, presumably 7 days/week for 40 weeks (duration-adjusted = 822 mg/cu.m). All animals survived the exposures.

The results from this study show that, under continuous exposure, the neurotoxicity of n-hexane is potentiated by MEK. n-Hexane-induced hindlimb paralysis and related neuropathology was manifest in all five animals after 9 weeks of exposure to 500 ppm n-hexane, 22 hours/day, 7 days/week (1616 mg/cu.m); similar clinical signs and neuropathology were present 1 week earlier in animals (incidence not given) exposed to the n-hexane/MEK mixtures. Complete hindlimb paralysis was already visible (incidence not given) after 4 weeks in the group exposed to 500 ppm n-hexane + 200 ppm MEK. These observations were accompanied by the anticipated neuropathological alterations (that is, giant axonal swellings in both central and peripheral sites).

Under the conditions of this study, clinical or neuropathological signs of

n-hexane neuropathy developed in animals exposed to 700 ppm n-hexane under continuous conditions (2262 mg/cu.m), but not under intermittent conditions to the same concentration. Thus, n-hexane-induced neuropathies appear sooner under conditions of continuous exposure than under intermittent exposure.

Respiratory tract lesions have been observed in rabbits (n=12) following both high-level acute (8 days) and longer-term (24 weeks) exposure to a single level of exposure to n-hexane vapors (Lungarella et al., 1984). The terminal bronchioles showed the most characteristic damage. In a subchronic study, rabbits (n=12) exposed to 3000 ppm (10,574 mg/cu.m), 8 hours/day, 5 days/week for 24 weeks (duration-adjusted = 2492 mg/cu.m) also developed exposure-related pulmonary lesions. Clinical signs of ocular and upper respiratory tract irritation and respiratory difficulties (such as gasping, lung rales, mouth breathing) were seen throughout the study in exposed rabbits. Neurologic effects were not investigated in this study, although mention is made in the discussion of this study that this species does not show any evidence of neuropathy after long-term exposure to n-hexane.

n-Hexane can cause testicular damage. Adult male Sprague-Dawley rats (number of animals is unclear, but is at least 48 total) were exposed to either air, 1000 ppm n-hexane (3525 mg/cu.m; duration-adjusted = 2644 mg/cu.m), 1000 ppm xylene, or 1000 ppm n-hexane + 1000 ppm xylene 18 hours/day, 7 days/week for 61 days (Nylen et al., 1989). Groups of six rats each from these exposure were sacrificed for morphological examination at 2 weeks, 10 months, and 14 months after termination of the exposure. Androgen biosynthesis, serum testosterone, vas deferens morphology, epididymal sperm morphology, and fertility were studied. There was total loss of the germ cell line in a fraction (not designated) of the animals up to 14 months post-exposure. Examination for neuropathies was not done in this study. A freestanding FEL is identified by this study at 3525 mg/cu.m x 18/24 hour x 7/7 days = 2644 mg/cu.m.

n-Hexane does not appear to be a teratogen. Pregnant albino rats exposed to 1000 ppm (3489 mg/cu.m, not duration adjusted) of 99% n-hexane vapor 6 hours/day during gestational days 8 to 16 had significantly depressed postnatal growth up to 3 weeks after birth, which returned to normal by 7 weeks; no difference in fetal resorption, birth weight or other abnormalities were noted (Bus et al., 1979). Marks et al. (1980) administered up to 9.9 g/kg/day by gavage to pregnant mice during gestational days 6 to 15 and observed no teratogenic effects, even at doses above the maximum tolerated dose for the dams. However, a reduction in fetal weight was dose-related at doses of 7.92 and 9.9 g/kg/day although no fetal malformations were observed. Five of 33 dams treated with 9.9 g/kg/day died. Thus, n-hexane was not teratogenic even at maternally toxic doses.

Mast et al. (1987) conducted an inhalation developmental toxicity study in rats. Concentrations of 0, 200, 1000, or 5000 ppm 99.9% n-hexane vapor (0, 705, 3525, or 17,623 mg/cu.m, not duration-adjusted) were administered to pregnant rats (30 sperm-positive and 10 virgin females/dose) 20 hours/day for 14 consecutive days on gestational days 6 to 19. Maternal toxicity (reduction in weight gain) was noted in all exposure groups, but was statistically significant only at the high-dose group. n-Hexane had no effect on the number of implantations, the mean percent of live pups per litter, the mean percent

of resorptions per litter, or on the fetal sex ratio compared to controls. There were no maternal deaths and no clinical signs of toxicity were noted. No significant differences were observed in intrauterine death rate, or in the incidence of fetal malformations. A statistically significant reduction in fetal body weight relative to controls was observed for males at the 1000-ppm (3525 mg/cu.m) and 5000-ppm (17,623 mg/cu.m) exposure levels (7 and 15% reduction, respectively). The lowest n-hexane concentration, 200 ppm (705 mg/cu.m) was a NOAEL for reduced fetal body weight. NOAEL(ADJ) = 705 mg/cu.m.

Litton Bionetics (1979) reported negative teratologic results when pregnant female rats (n=20) were exposed to graded concentrations of 0, 100 or 400 ppm n-hexane 6 hours/day (0, 352, or 1410 mg/cu.m, not duration-adjusted) on gestational days 6 through 15.

Two studies by Mast et al. showed no effect on reproductive tests in male mice after exposure to n-hexane at 0, 200, 1000, or 5000 ppm (0, 705, 3525, or 17,624 mg/cu.m) 20 hours/day for 5 consecutive days (duration-adjusted = 0, 420, 2096, or 10,484 mg/cu.m). Twenty mice per dose level were used in a sperm morphology study, 30/group in a male dominant lethal study. In the sperm morphology study (Mast et al., 1989a), the animals were examined during the fifth post-exposure week. In the male dominant lethal study (Mast et al., 1989b), 10 mice from each group were sacrificed 1 day after exposure for evaluation of the germinal epithelium. The remaining 20 mice were mated with unexposed virgin females for 8 weekly intervals (new females provided each week). The mated females were then sacrificed 12 days after the last day of cohabitation and their reproductive status and the number and viability of the implants noted.

___I.B.5. CONFIDENCE IN THE INHALATION RfC

Study -- Medium
Data Base -- Medium
RfC -- Medium

Despite the small sample size, the epidemiological study of Sanagi et al. (1980) is given a medium confidence rating, since the LOAEL in this study was based on neurotoxicology and this endpoint is supported by numerous other subchronic inhalation studies in animals and by human occupational studies. The confidence rating in the data base for n-hexane is rated only as medium because of the lack of long-term inhalation studies and appropriate reproductive studies. A medium confidence rating for the RfC follows.

___I.B.6. EPA DOCUMENTATION AND REVIEW OF THE INHALATION RfC

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- None

Agency Work Group Review -- 04/19/90

Verification Date -- 04/19/90

___I.B.7. EPA CONTACTS (INHALATION RfC)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX) or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- n-Hexane
CASRN -- 110-54-3

Not available at this time.

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_VI. BIBLIOGRAPHY

Substance Name -- n-Hexane
CASRN -- 110-54-3
Last Revised -- 07/01/90

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None

__VI.B. INHALATION RfD REFERENCES

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__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

None

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_VII. REVISION HISTORY

Substance Name -- n-Hexane
CASRN -- 110-54-3

Date	Section	Description
07/01/90	I.B.	Inhalation RfC summary on-line
07/01/90	VI.	Bibliography on-line
02/01/91	I.B.	Text edited
09/01/91	II.	Carcinogenicity assessment now under review
07/01/93	I.B.1.	LOAEL(HEC) added

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SYNONYMS

Substance Name -- n-Hexane
CASRN -- 110-54-3
Last Revised -- 07/01/90

110-54-3
AI3-24253
ESANI [ITALIAN]
HEKSAN [POLISH]
HEXANE
N-HEXANE
HEXANEN [DUTCH]
HSDB 91
NCI-C60571
SKELLYSOLVE B

n-Hexane; Downloaded 8/13/97

n-Hexane; Downloaded 8/13/97

0118
Toluene; CASRN 108-88-3 (03/01/97)

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Toluene

File On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	04/01/94
Inhalation RfC Assessment (I.B.)	on-line	08/01/92
Carcinogenicity Assessment (II.)	on-line	02/01/94

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Toluene
CASRN -- 108-88-3
Last Revised -- 04/01/94

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this

substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Changes in liver and kidney weights 13-Week Rat Gavage Study NTP, 1989	NOAEL: 312 mg/kg converted to 223 mg/kg/day LOAEL: 625 mg/kg converted to 446 mg/kg/day	1000	1	2E-1 mg/kg/day

*Conversion Factors: Dose adjusted for gavage schedule of 5 days/week.

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

NTP (National Toxicology Program). 1989. Toxicology and Carcinogenesis Studies of toluene in F344/N rats and B6C3F1 mice. Technical Report Series No. 371. Research Triangle Park, NC.

The oral toxicity of toluene was investigated in this subchronic gavage study in F344 rats. Groups of 10 rats/sex/group were administered toluene in corn oil at dosage levels of 0, 312, 625, 1250, 2500, or 5000 mg/kg for 5 days/week for 13 weeks. All animals receiving 5000 mg/kg died within the first week. One female and 8 males in the 2500 mg/kg group died, but 2 of these were due to gavage errors. No deaths occurred at lower doses. Several toxic effects were noted at doses greater than or equal to 2500 mg/kg, including prostration, hypoactivity, ataxia, piloerection, lacrimation, excessive salivation, and body tremors. No signs of biologic significance were seen in groups receiving less than or equal to 1250 mg/kg. The only significant change in body weight was a decrease ($p<0.05$) for males in the 2500 mg/kg group. There were no toxicologically significant changes in hematology or urinalysis for any group of animals. Biochemical changes, including a significant increase ($p<0.05$) in SGOT in 2500 males and a dose-related increase in cholinesterase in females receiving 2500 and 5000 mg/kg, were not considered to be biologically significant. There were several pathologic findings and organ weight changes in the liver, kidney, brain, and urinary bladder. In males, absolute and relative weights of both the liver and kidney were significantly increased ($p<0.05$) at doses greater than or equal to 625 mg/kg. In females, absolute and relative weights of the liver, kidney, and heart were all significantly increased at doses greater than or equal to 1250 mg/kg ($p<0.01$ for all comparisons except $p<0.05$ for absolute kidney and heart weights at 1250 mg/kg). Histopathologic lesions in the liver consisted of hepatocellular hypertrophy, occurring at greater than or equal to 2500 mg/kg. Nephrosis was observed in rats that died, and damage to the tubular epithelia of the kidney occurred in terminally sacrificed rats. Histopathologic changes were also noted in the brain and urinary bladder. In the brain, mineralized

foci and necrosis of neuronal cells were observed in males and females at 2500 mg/kg and males at 1250 mg/kg. In the bladder, hemorrhage of the muscularis was seen in males and females at 5000 mg/kg and males at 2500 mg/kg. The NOAEL for this study is 312 mg/kg/day based on liver and kidney weight changes in male rats at 625 mg/kg. The toxicologic significance of these organ weight changes is strengthened by the occurrence of histopathologic changes in both the liver and kidney at higher doses. Because the exposure was for 5 days/week, this dose is converted to 312 x 5/7 = 223 mg/kg/day. The LOAEL is 625 mg/kg, which is 446 mg/kg/day when converted.

NTP (1989) also conducted a 13-week gavage study in B6C3F1 mice, following the same regimen described above. All mice receiving 5000 mg/kg died and 8/20 receiving 2500 mg/kg also died. Signs of toxicity seen in animals receiving greater than or equal to 2500 mg/kg included subconvulsive jerking, prostration, impaired grasping reflex, bradypnea, hypothermia, ataxia, and hypoactivity. By week 13, the mean body weight of 2500 mg/kg males was significantly ($p<0.05$) lower than controls. No other significant changes were reported for any group, including macroscopic observation, organ weight means, or clinical pathology parameters. The NOAEL for mice in this study was 1250 mg/kg.

The subchronic study by Wolf et al. (1956) is supportive of the NTP studies. Groups of 10 female Wistar rats were administered gavage doses of 0, 118, 354, or 590 mg/kg toluene dissolved in olive oil. A total of 138 doses were administered over 193 days, resulting in average doses of approximately 0, 84, 253, or 422 mg/kg/day. Hematologic, behavioral, gross and histopathologic examinations were conducted with no toxic effects being reported at any dose. Therefore, the highest dose of 422 mg/kg/day is considered to be the NOAEL for this study. However, this study is not used as the basis for the RfD because the LOAEL of 446 mg/kg/day identified by NTP (1989) is too close to the NOAEL identified by Wolf et al. (1956). Also, the NTP study indicated that male rats are more sensitive to toluene and the Wolf study utilized only female rats.

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF -- An uncertainty factor of 1000 was applied to account for inter- and intraspecies extrapolations, for subchronic-to-chronic extrapolation and for limited reproductive and developmental toxicity data.

MF -- None

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

Kostas and Hotchin (1981) exposed NYLAR mice pre- and post-natally to toluene provided in the drinking water at concentrations of 0, 16, 80, or 400 ppm. Effects were noted in all dosed groups on rotorod performance, measured at 45 to 55 days of age, but there was an inverse dose-response relationship. No effects of toluene exposure were seen on maternal fluid consumption, offspring

mortality rate, development of eye or ear openings, or surface-righting response. This study is not suitable for use in risk assessment because only 6 to 9 pregnancies/dose group were obtained, and because the dose-response relationship was inverse.

In an abstract providing limited information, Nawrot and Staples (1979) reported an increase in embryonic lethality in mice exposed to toluene from days 6 to 15 of gestation. Pregnant CD-1 dams were administered 0.3, 0.5, or 1.0 mL/kg bw, 3 times/day (equivalent to approximately 780, 1300, or 2600 mg/kg/day). Maternal toxicity was not observed at any dose level, but toluene was shown to be teratogenic at the high dose and embryolethal at the low dose. These levels are higher than the NOAEL demonstrated by the NTP (1989) study.

Several subchronic and chronic inhalation studies have been performed on toluene but are not considered to be suitable for deriving an oral RfD. These studies are summarized nicely in the introduction to the 2-year inhalation bioassay by NTP, 1989. The studies identify the following potential target organs: kidney (male rat); hematologic effects (mice); central nervous system (rats, mice, primates); developmental toxicity (rats, rabbits). It is beyond the scope of this oral RfD summary sheet to describe each of these studies, but the two chronic (2 year) inhalation studies are summarized briefly below.

In a 2-year inhalation study by NTP (1989), F344 rats (60/sex/group) were exposed to 0, 600, or 1200 ppm toluene and B6C3F1 mice (60/sex/group) to 0, 120, 600, or 1200 ppm toluene for 6.5 hours/day, 5 days/week. Ten animals/group (except male mice) were removed at 15 months for toxicologic evaluation. At 15 months, there was an increased incidence and severity of nonneoplastic lesions of the nasal cavity of exposed rats. Minimal hyperplasia of the bronchial epithelium was seen in 4/10 female mice at 1200 ppm. There were no significant differences in survival among any group of animals during the 2-year study. Mean body weights were generally similar for all groups throughout the study. Nephropathy was seen in almost all rats with the severity somewhat increased in exposed rats. There were also effects on the olfactory and respiratory epithelia of exposed rats. No biologically important lesions were seen in any groups of mice. There was no evidence of carcinogenicity for any group of animals in this study.

A chronic inhalation study in rats performed by CIIT (1980) failed to produce an adverse effect. Groups of 40 F344 rats/sex were exposed to 30, 100, or 300 ppm toluene for 6 hours/day, 5 days/week for 24 months. An unexposed group of 120 rats/sex served as a control. Clinical chemistry, hematology, and urinalysis testing were conducted at 18 and 24 months. All parameters measured at the termination of the study were normal except for a dose-related reduction in hematocrit values in females exposed to 100 and 300 ppm toluene. The highest dose of 300 ppm was considered to be a NOAEL.

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: High
Data Base: Medium
RfD: Medium

Confidence in the principal study is high because a sufficient number of animals/sex were tested in each of six dose groups (including vehicle controls) and many parameters were studied. The same protocol was tested in both mice and rats, with rats being identified as the more sensitive species. The data base is rated medium because it is supported by a 6-month oral study. It is not higher than medium because there is no reproductive study. Also, the oral studies are all subchronic, with the critical study being only 13 weeks in duration. Medium confidence in the RfD follows.

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- None

Agency Work Group Review -- 05/20/85, 08/05/85, 08/05/86, 05/17/90, 06/20/90

Verification Date -- 06/20/90

___I.A.7. EPA CONTACTS (ORAL RfD)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX) or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Toluene
CASRN -- 108-88-3
Last Revised -- 08/01/92

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to

Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

___I.B.1. INHALATION RfC SUMMARY

Critical Effect	Exposures*	UF	MF	RfC
Neurological effects Occupational Study Foo et al., 1990	NOAEL: None mg/cu.m LOAEL: 332 mg/cu.m (88 ppm) LOAEL(ADJ): 119 mg/cu.m LOAEL(HEC): 119 mg/cu.m	300	1	4E-1
Degeneration of nasal epithelium 2-Year Rat Chronic Inhalation Study NTP, 1990	NOAEL: None LOAEL: 2261 mg/cu.m (600 ppm) LOAEL(ADJ): 437 mg/cu.m LOAEL(HEC): 79 mg/cu.m			

*Conversion Factors: MW = 92.15.

Foo et al., 1990: Assuming 25 C and 760 mmHg, LOAEL (mg/cu.m) = 88 ppm x 92.15/24.45 = 332 mg/cu.m. This is an extrarespiratory effect of a soluble vapor. The LOAEL is based on an 8-hour TWA occupational exposure. MVho = 10 cu.m/day, MVh = 20 cu.m/day. LOAEL(HEC) = LOAEL(ADJ) = 332 x MVho/MVh x 5 days/7 days = 119 mg/cu.m.

NTP, 1990: Assuming 25 C and 760 mmHg, LOAEL (mg/cu.m) = 600 ppm x 92.15/24.45 = 2261 mg/cu.m. LOAEL(ADJ) = LOAEL (mg/cu.m) x 6.5 hours/24 hours x 5 days/7 days = 437 mg/cu.m. The LOAEL(HEC) was calculated for a gas:respiratory effect in the extrathoracic region. MVa = 0.24 cu.m/day, MVh = 20 cu.m/day, Sa (ET) = 11.6 sq.cm, Sh (ET) = 177 sq.cm. RGDR = (MVa/Sa) / (MVh/Sh) = 0.18. LOAEL(HEC) = 437 x RGDR = 79 mg/cu.m.

___I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

Foo, S., J. Jeyaratnam and D. Koh. 1990. Chronic neurobehavioral effects of toluene. Br. J. Ind. Med. 47(7): 480-484.

NTP (National Toxicology Program). 1990. Toxicology and carcinogenesis studies of toluene in F344/N rats and B6C3F1 mice (inhalation studies). NTP-TR-371. 253 p.

In humans, toluene is a known respiratory irritant with central nervous system (CNS) effects. Because available studies could not provide subthreshold (NOAEL) concentrations for either of these effects, the LOAELs for both effects need to be considered in developing the RfC. Consequently, the study of Foo et al. (1990) was used for the CNS effects, and that of the National Toxicology Program (NTP, 1990) for the irritant effects. Because the CNS effect was judged to be a more severe and relevant endpoint, the LOAEL for this effect was used for deriving the RfC. Further, this effect is supported by a number of other occupational studies that show effects around 100 ppm.

Foo et al. (1990) conducted a cross-sectional study involving 30 exposed female workers employed at an electronic assembly plant where toluene was emitted from glue. Toluene levels reported in the study were from personal sample monitoring and reported as an 8-hour TWA, although the number of samples taken and the actual sampling period were not given. No historical exposure values were given. Co-exposure to other solvents was not addressed in the study. The exposed and control cohorts were matched for age, ethnicity, and use of medications. Members of these cohorts did not use alcohol and were nonsmokers. Medical histories were taken to eliminate any histories of central or peripheral nervous system disorders. The average number of years (+/- SD) worked by the exposed population was 5.7 +/- 3.2 and by the controls was 2.5 +/- 2.7. Exposed workers breathed toluene air levels of 88 ppm (332 mg/cu.m) as a TWA and control workers 13 ppm (49 mg/cu.m) (TWA); both of which are averages of the individual personal samples. A battery of eight neurobehavioral tests were administered to all exposed and control workers. The tests were performed midweek, before the workers reported to their stations for the day. Group means revealed statistically significant differences in 6/8 tests; all tests showed that the exposed workers performed poorly compared with the control cohort. When individual test results were linearly regressed against personal exposure concentrations, poor concentration-response relationships resulted for the six tests, with correlation coefficients ranging from 0.44 to 0.30. Irritation effects were not evaluated in this study, and no clinical signs or symptoms were reported. The paucity of exposure information, coupled with the small size of the cohort, limits the interpretation of this study, although the results were essentially confirmed in a clinical study in which the toluene concentrations were carefully controlled (Echeverria et al., 1989) at levels bracketing 88 ppm. Although the data in Echeverria et al. (1989) were generated from short-term exposures (3-7 hours over a period of 142 days), the results may be considered relevant to longer-term exposures as several studies indicate the absence of a duration-response relationship in toluene-induced symptomatology. Fornazzari et al. (1983) noted the absence of a duration-effect relationship among toluene abusers when they were segregated into neurologically impaired vs. unimpaired ($p = 0.65$). The human studies of Iregren (1982), Cherry et al. (1985), Baelum et al. (1985), and the principal study of Foo et al. (1990) all report this lack of a duration-response relationship and confirm the occurrence of CNS effects. Foo et al. (1990) indicate a LOAEL of 88 ppm toluene (332 mg/cu.m) for neurobehavioral changes from chronic exposure to toluene.

In a 2-year bioassay, Fischer 344 rats (60/sex/group) were exposed to 0, 600, or 1200 ppm (0, 2261, or 4523 mg/cu.m, respectively) toluene vapors, 6.5

hours/day, 5 days/week (duration-adjusted to 0, 437, and 875 mg/cu.m, respectively) for 103 weeks (NTP, 1990). To generate toluene vapor, the liquid material was heated, and the vapor diluted with nitrogen and mixed with the chamber ventilation air. An interim sacrifice was carried out at 15 months on control and 1200-ppm groups (10/sex/group) to conduct hematology and histopathology of the brain, liver, and kidney. Body weights were measured throughout the study. Gross necropsy and micropathology examinations were performed at the end of the study on all major organs including the nasal passage tissues (three sections), lungs, and mainstem bronchi. Mean body weights in both exposed groups were not different from controls for either sex. No exposure-related clinical signs were reported, and survival rate was similar for all groups. At the interim sacrifice, there was a mild-to-moderate degeneration in the olfactory and respiratory epithelium of the nasal cavity in 39/40 rats of the 600- and 1200-ppm groups compared with 7/20 controls. At the end of 2 years, there was a significant ($p<0.05$) increase in the incidence of erosion of the olfactory epithelium (males: 0/50, 3/50, and 8/49; females: 2/49, 11/50, and 10/50; at 0, 600, and 1200 ppm, respectively) and of degeneration of the respiratory epithelium (males: 15/50, 37/50, and 31/49; females: 29/49, 45/50, and 39/50; at 0, 600, and 1200 ppm, respectively) in the exposed animals. The females exposed to 600 and 1200 ppm also exhibited a significant increase in inflammation of the nasal mucosa (27/49, 42/50, and 41/50 at 0, 600, and 1200 ppm, respectively) and respiratory metaplasia of the olfactory epithelium (0/49, 2/50, and 6/50 at 0, 600, and 1200 ppm, respectively). A LOAEL of 600 ppm toluene was determined for the concentration-dependent increase in erosion of the olfactory epithelium in male rats and the degeneration of the respiratory epithelium in both sexes. No NOAEL could be derived from this study.

___I.B.3. UNCERTAINTY AND MODIFYING FACTORS (INHALATION RfC)

UF -- An uncertainty factor of 10 is used to account for intraspecies variability and another factor of 10 for the use of a LOAEL. An additional factor of 3 is applied for data base deficiencies, including the lack of data and well-characterized laboratory animal exposures evaluating neurotoxicity and respiratory irritation.

MF -- None

___I.B.4. ADDITIONAL STUDIES / COMMENTS (INHALATION RfC)

Toluene-induced neurotoxicity has been documented in humans over a broad spectrum of severity that correlates well with concentration. Numerous case studies on chronic toluene abusers [repeatedly exposed to greater than 30,000 ppm (113,000 mg/cu.m)] have demonstrated functional deficits of the CNS accompanied by abnormal morphology of cerebellar and cortical areas of the brain. Under acute exposure conditions [short exposures to greater than 10,000 ppm (37,690 mg/cu.m)], toluene produces CNS narcosis [American Conference of Governmental Industrial Hygienists (ACGIH), 1991]. Lower concentrations, i.e., 800-400 ppm (3015-1508 mg/cu.m), have been associated

with worker complaints of CNS-related effects (ACGIH, 1991). Clinical studies using controlled exposure to toluene have demonstrated concentration-related occurrence of complaints such as drowsiness, ataxia, visual impairment, and headache. A number of occupational studies indicate that these same effects are present in exposed worker populations at concentrations lower than 400 ppm (1508 mg/cu.m) although deficiencies in most of these studies preclude confirming this finding unequivocally. Descriptions of a number of these studies follow. The preponderence of the literature showing CNS effects and the well-known proclivity for solvents to affect CNS processes in humans leave little doubt that the brain is a principal target organ for toluene toxicity in humans.

In cases of inhalation abuse of toluene, Rosenberg et al. (1988) demonstrated diffuse cerebral, cerebellar, and brainstem atrophy in 3 of 11 toluene abusers who also had neurological abnormalities. Filley et al. (1990) were able to correlate neuropsychological impairment with the degree of white matter abnormality ($p<0.01$). Cerebellar and cortical functions were classified as impaired in 15/24 individuals who had abused toluene daily (425 +/- 366 mg/day) for extended periods (6.3 +/- 3.9 years) (Fornazzari et al., 1983). In a limited case study, Metrick and Brenner (1982) demonstrated brainstem atrophy through computerized tomographic scans and abnormal brainstem auditory-evoked potentials in 2/2 chronic toluene abusers (12-16 years of admitted, continuous abuse). These studies confirm the occurrence of severe CNS damage in response to highly abusive concentrations of toluene.

Several studies that have investigated the occurrence of neurotoxicity at lesser concentrations, such as occupational situations, have not demonstrated significant neurological or other effects. Hanninen et al. (1987) performed a battery of 11 psychological tests on 43 printing workers who had been occupationally exposed to approximately 117 ppm (441 mg/cu.m) toluene for an average of 22 years and found only mildly adverse effects in 2/11 tests. The control and exposed cohorts in this study were, however, mismatched in several areas, most notably alcohol use. Iregren (1982) examined the psychological performance of 38 printers who had been occupationally exposed to 50-150 ppm (188-565 mg/cu.m) toluene for an average of 16.3 years (range 3-32 years). No effects were seen, although the cohorts in this study were apparently matched only by age. In a cohort study, Cherry et al. (1985) attempted to better match the control and exposed cohorts and considered alcohol use. Although no differences between the cohorts were statistically significant, the exposed workers performed worse than the nonexposed workers on 10/13 psychological tests. The 52 workers in this study were not, however, rigorously matched, and the concentrations listed in the study ranged up to greater than 500 ppm (1884 mg/cu.m). The cohorts in the study of Foo et al. (1990) were well matched for a number of confounders, including alcohol use, and statistically significant psychological effects were seen.

In the occupational study conducted by Yin et al. (1987), 94 solvent workers (38 men and 56 women; average employment duration, 6.8 years) and 138 controls (48 men and 90 women) were examined for exposure using diffusion dosimeters, subjective symptoms by questionnaire, hematology, and urinalysis. Exposure concentration (7-hour mean TWA) in the workers was estimated at 42.8 ppm (161 mg/cu.m) toluene with a maximum measurement of 123 ppm (464 mg/cu.m). Workers were co-exposed to 1.3 ppm benzene. No exposure-related effects were

noted in any of the biochemical tests examined. In considering the prevalence of subjective symptoms (sore throat, headaches, and dizziness) workers were subgrouped into low (6-39 ppm, n = 28) and high (40-123 ppm, n = 29) categories. Although the prevalence of subjective symptoms was significantly higher in the exposed workers compared with the control cohort ($p<0.01$), a concentration-response relationship was not discernable among the groups. No other treatment-related effects were reported. The study was limited because the exposed and unexposed groups were not matched to control for confounding effects (e.g., age, smoking, alcohol consumption, exposure duration). Based on these results, exposure to an average of approximately 42.8 ppm toluene produced no biochemical abnormalities, although neither respiratory irritation nor psychological performance was directly evaluated in these workers.

In the occupational study by Lee et al. (1988), prevalence of subjective symptoms was categorized with respect to exposure levels. The study population (193 women and 65 controls) completed a questionnaire. The exposures were reported as 8-hour TWAs, and workers were grouped in exposure categories of nonexposed, 1-50 ppm, 51-100 ppm, 101-150 ppm, and more than 151 ppm (duration of exposures was not reported). A concentration-dependent increase in prevalence was reported for 25/67 symptoms with increases in complaints over controls occurring at around 100 ppm (348 mg/cu.m). Similar to the Yin et al. study (1987) reported above, symptomatology included headaches, sore throats, and dizziness. Although an effect level in humans of around 100 ppm is indicated by this study, no objective measures of toxicity were examined.

A number of acute human studies have focused on toluene effects. In general, these studies corroborate subjective CNS effects such as headaches and dizziness reported in other longer-term occupational studies (Yin et al., 1987; Lee et al., 1988) and also document irritation effects. The study of Echeverria et al. (1989) correlates the occurrence of these subjective effects with substantial neurological symptoms.

Forty-two college students (21 female and 21 male) were exposed to 0, 74 ppm (279 mg/cu.m), or 151 ppm (569 mg/cu.m) toluene for 7 hours over 3 days (Echeverria et al., 1989). This exposure sequence was repeated for a total of 42 exposures over a 3-month period. The odor of toluene was masked. A battery of performance tests was administered to each participant prior to starting the exposures and again at 4 and 7 hours during the exposure; the initial test served as a control for those tests performed during the exposure. A 5-10% decrement in performance was considered significant if consistent with a linear trend. Test results for visual perception differed from control values for both exposure levels. Results of a manual dexterity test differed from control values at the higher but not the lower exposure level. Psychomotor test results were unaffected by toluene exposure. Subjective symptomatology increased with exposure with increasing numbers of complaints of eye irritation, headache, and somnolence. A NOAEL of 74 ppm (279 mg/cu.m) is indicated for these results. The duration-adjusted value is 122 mg/cu.m for these acute effects.

Andersen et al. (1983) exposed 16 subjects (average age of 24 years) to 0, 10, 40, or 100 ppm (0, 38, 151, or 377 mg/cu.m) toluene for 6 hours on each of 4 consecutive days. Individuals were tested for nasal mucous flow, lung

function, subjective response, and psychometric performance. At 100 ppm, irritation was experienced in the eyes and nose, but no effect on nasal mucous flow or lung function was observed. The subjects frequently reported headaches, dizziness, and a feeling of intoxication. These effects were not reported by the 10- or 40-ppm exposure groups. No effects were seen in performance tests. This study indicates an effect level of 100 ppm, and a NOAEL of 40 ppm (151 mg/cu.m).

The acute study by Baelum et al. (1990) evaluated 32 males and 39 females exposed to 0 or 100 ppm (0 or 377 mg/cu.m), or to varying exposures of 50-300 ppm (188-1131 mg/cu.m) (TWA = 102 ppm), for 7 hours. Volunteers exercised on an ergometer cycle for 3 periods of 15 minutes each during the exposure. No significant differences were found in the performances between the exposed and control groups in a battery of tests for performance, visual attention, and reaction times. Exposed subjects reported an increase over nonexposed subjects ($p<0.1$) in nose and lower respiratory irritation, feelings of intoxication, dizziness, increased coughing, and headaches. Differences were not noted between the group exposed to a constant level (100 ppm) and the group exposed to the same TWA, but with peaks of up to 300 ppm.

Baelum et al. (1985) investigated the effects of a 6.5-hour toluene exposure to 43 printers with a long-term occupational exposure to a mixture of solvents including toluene and 43 controls with no history of exposure to solvents or other chemicals. The duration of employment for the workers ranged from 9-25 years. Each individual was exposed only once to either 0 or 100 ppm (0 or 377 mg/cu.m) toluene during a 6.5-hour exposure period, preceded by a 1-hour acclimatization period. These subjects were then subgrouped into printers exposed to toluene (n = 20), printers exposed to air (n = 23), controls exposed to toluene (n = 21), and controls exposed to air (n = 22). All subjects carried out a battery of tests for psychometric performance, visual perception, and vigilance evaluation. Both printers and controls complained of nasal and eye irritation, unacceptable air quality, and unacceptable odor level during the toluene exposure. Signs of neurotoxicity, including moderate fatigue, sleepiness, headaches, and a feeling of intoxication, were likewise similarly reported for both groups. A significant decrease in performance was found for the pegboard visual motor function test in the exposed printers, but not in the controls exposed to 100 ppm toluene. A decrease in psychometric performance, primarily in visual perception and accuracy, was observed in toluene-exposed individuals. Acute exposure to toluene resulted in a lower performance in 4/10 tests conducted, 3 of these 4 evaluated visual perception. The most profound difference between subjects exposed to 100 ppm toluene and those exposed to clean air was observed in the color discrimination test; this difference was seen in both exposed vs. nonexposed printers and exposed vs. nonexposed controls. This study indicates that little tolerance develops to the irritative and central effects in humans exposed to toluene and that 100 ppm (377 mg/cu.m) is the effect level for these symptoms.

Von Oettingen et al. (1942) exposed 3 humans to 100 or 200 ppm (377 or 754 mg/cu.m) toluene vapors for 8 hours. At 200 ppm, the subjects experienced muscular weakness, confusion, impaired coordination, and dilated pupils, with after-effects including fatigue, general confusion, and moderate insomnia. In 1 subject exposed to 100 ppm toluene, moderate fatigue, sleepiness, and

headaches were reported.

Hepatotoxicity has also been examined as a toxicologic endpoint of toluene exposure in humans. Fornazzari et al. (1983) described moderate elevation of serum AP levels in 13/24 (and SGOT in 7/24) toluene abusers upon admission to a clinic. These elevated levels were normal after 2 weeks of solvent abstinence, although the accompanying CNS effects were only minimally improved. In a cross-sectional study of 181 printing workers in which toluene exposures were less than 200 mg/cu.m, no adverse effects were apparent as judged from serum liver enzymes (Boewer et al., 1988). In another cross-sectional occupational study conducted by Guzelian et al. (1988) that involved 289 printing factory employees, 8 workers were found who had an increase described as "marked" in the ratio of ALT/AST enzyme serum activity. Biopsies revealed mild pericentral fatty livers in each of the eight cases. Based on environmental data (probably area monitors) the levels of toluene to which these workers were exposed was less than 200 mg/cu.m., 2-8 hours/day.

Fischer 344 rats (120/sex/group) inhaled 0, 30, 100, or 300 ppm (0, 113, 377, or 1130 mg/cu.m, respectively) toluene (99.9% purity), 6 hours/day, 5 days/week (duration-adjusted to 0, 20, 67, or 202 mg/cu.m, respectively) for 106 weeks (CIIT, 1980; Gibson and Hardisty, 1983). Vapor, generated by bubbling clean air through toluene, was passed through the air supply duct and mixed with air by turbulent flow to produce the desired concentration. Hematology, blood chemistry, and urinalysis were conducted in all groups at 6 (5/sex), 17 (5/sex), 18 (10-20/sex), and 24 months (10/sex). Histopathology was evaluated only in the control and 300-ppm groups at 6 (5/sex), 12 (5/sex), and 18 months (20/sex). At 24 months, histopathological examinations were conducted in organs of all surviving animals, including the respiratory system and sections through the nasal turbinates (number not indicated). No treatment-related non-neoplastic effects were observed in the exposed animals. Although the male rats exposed to 300 ppm had a significant increase in body weight compared to controls, no concentration-response was evident. At the end of the exposure period, the female rats exposed to 100 or 300 ppm exhibited a slight but significant reduction in hematocrit; an increase in the mean corpuscular hemoglobin concentration was also noted but only in the females exposed to 300 ppm. The highest concentration examined in this study, 300 ppm, is designated as a NOAEL for toxicity remote from the respiratory tract in rats. CIIT (1980) reported that the technical and raw data were not audited by their quality assurance group during the study period, although CIIT did conduct a quality assessment procedure to review the data. The available pathology reports containing these data indicate that at least the lower respiratory tract was examined. Communication with the testing sponsor has provided information indicating that only one section was examined from the nasal cavity of these test animals. It is not clear whether this single section would have been sufficient to elucidate the areas of lesions noted in the NTP (1990) study. Consequently, the designation of the 300-ppm exposure level as a NOAEL for respiratory lesions (see NTP,1990) is problematic.

Fischer 344/N rats (10/sex/group) were exposed to toluene vapors at 0, 100, 625, 1250, 2500, and 3000 ppm (0, 377, 2355, 4711, 9422, and 11,307 mg/cu.m, respectively) 6.5 hours/day, 5 days/week (duration-adjusted to 0, 73, 455, 911, 1823, and 2187 mg/cu.m, respectively) for 15 weeks (NTP, 1990). Organ weights were measured and histological examinations were performed only

on controls, 2500- and 3000-ppm groups, and animals that died before the end of the study. Eight of 10 males exposed to 3000 ppm died, all during the 2nd exposure week. No females died at any exposure level. Compared to the controls, final body weights were 15 and 25% lower in the males and 15 and 14% lower in the females of the 2500- and 3000-ppm groups, respectively. There was a concentration-related increase in the relative liver weight, significant at 1250, 2500, and 3000 ppm in males and at 2500 and 3000 ppm in females. The relative weights of the heart, lung, kidney, and right testis were also significantly elevated in the 2500- and 3000-ppm animals compared to those of the controls, although no histopathology was observed in any exposure group. Toxic effects noted in a concurrently conducted gavage study (urinary bladder hemorrhages in the two highest exposure groups) were not noted in this subchronic inhalation study. A LOAEL of 2500 ppm [LOAEL(HEC) = 1823 mg/cu.m] was determined for the decrease in body weight gain in both males and females, and the NOAEL for this effect was 1250 ppm [NOAEL(HEC) = 911 mg/cu.m].

Toluene has been suspected to cause congenital defects in infants born to mothers who were exposed to or who abused toluene during pregnancy. In a case report study, Hersh et al. (1985) describes clinical and morphometric characteristics common to 3 children whose mothers had abused toluene (but apparently not alcohol or any other substance) for a period of 4-5 years including during their pregnancies with the affected children. Clinical findings common to these three children included microcephaly, CNS dysfunction, attention deficits, and developmental delay/mental deficiency. Phenotypic similarities included a small midface, deep-set eyes, micrognathia (smallness of the jaws), and blunting of the fingertips. A retrospective cohort study was conducted by McDonald et al. (1987) who examined the history of exposure to chemicals of 301 women who had recently given birth to an infant with an important congenital defect. An identical number of women (referents) who had given birth to normal children were matched with respect to age, employment (hours/week), date of delivery, and educational level. In initial matched-pair analysis, chemical exposure was higher in the cases than in the referents (63 cases:47 referents) due to excess cardiac and miscellaneous defects. In further analysis by chemical categories, only exposure to aromatic solvents showed a clear excess of defects, mostly in the urinary tract. Details of these cases (n = 19) showed that toluene was identified as the solvent in 11 of these cases.

Hudak and Ungvary (1978) exposed three groups of pregnant CFY rats to toluene during different periods of gestation and for different durations of exposure. Two of the groups had their own control group exposed to air only and matched for period and daily duration. The first of these (n = 19) was exposed to 1500 mg/cu.m for 24 hours/day during gestational days 9 to 14. Two dams died during these exposures. No details on the deaths are given but no other maternal toxicity was observed. Fetotoxicity was also in evidence as sternebral alterations (6% vs. 1% in controls), extra ribs (22% vs. 0% in controls), and the presence of fetuses with missing tails (2/213, none observed in 315 controls) were recorded. Under these exposure conditions, 1500 mg/cu.m is a LOAEL for fetotoxicity and a frank effect level (FEL) for maternal toxicity. The second group (n = 14) received this same concentration continuously but on days 1-8 of gestation. Five dams died under these exposure conditions although toxicity parameters of the surviving dams were identical with the controls from the first group (gestational days 9-14). Slight

hydrocephaly was noted in 4 fetuses (all from the same litter), and 17% growth retardation was noted vs. 7% in the controls. Thus these exposure conditions are a FEL for maternal toxicity and a LOAEL for fetotoxicity. A third group was exposed to 1000 mg/cu.m for 8 hours/day from the 1st to the 21st day of gestation. No maternal deaths or toxicity occurred. Minor skeletal retardation was present in the exposed fetuses at a higher incidence rate (25%) than in concurrent controls (0%). These results indicate that 1000 mg/cu.m is a LOAEL for developmental effects under these exposure conditions. This concentration is also a NOAEL for maternal effects. These workers also exposed groups of pregnant CFLP mice (n = 11-15) to either air or 1500 or 500 mg/cu.m toluene continuously during days 6-13 of pregnancy. All mice exposed to the high concentration died within 24 hours of the beginning of exposure. No dams died in the lower exposure group. In this group, the average fetal weight decreased to 0.96 g from the average control weight of 1.07 g, and the percentage of weight-retarded fetuses (less than 0.9 g) increased to 27.6% from 6.5% in the controls. No difference in incidence of skeletal malformations or anomalies was noted between these and control fetuses. For mice, 1500 mg/cu.m is an FEL and 500 mg/cu.m is a mild LOAEL. Since duration adjustment is not performed for developmental effects, this concentration is also the LOAEL(HEC).

B6C3F1 mice (60/sex/group) were exposed to 0, 120, 600, or 1200 ppm (0, 452, 2261, or 4523 mg/cu.m, respectively) toluene 6.5 hours/day, 5 days/week (duration-adjusted to 0, 87, 47, and 875 mg/cu.m, respectively) for 2 years (NTP, 1990). Mean body weights were not significantly different among groups and no treatment-related clinical signs were observed. Deaths (moribund and natural) occurred in all exposure groups but were not related to exposure and were not greater than the control rates. An excess incidence of non-neoplastic inflammatory lesions of the urinary and genital system was observed in all the groups of male mice. At the 15-month interim sacrifice, minimal hyperplasia in the bronchial epithelium was observed in 4/10 females exposed to 1200 ppm. At the end of the study, there was a concentration-dependent increase in the incidence of splenic pigmentation in the exposed males (9/60, 11/60, and 18/59 at 120, 600, and 1200 ppm, respectively) compared to controls (4/60). In the females, the incidence was 37/50, 33/50, 34/49, and 28/47 at 0, 120, 600, and 1200 ppm, respectively. The occurrence of endometrial hyperplasia was present in 14% of the animals exposed to the highest concentration but only in 4% in the low-exposure groups and controls. No differences were noted between the exposed and control mice of either sex in the incidence of degeneration of either the olfactory or respiratory epithelium. No other non-neoplastic lesions were observed in exposed mice. As no adverse effects were noted in this study, the highest concentration, 1200 ppm was designated as a NOAEL in mice for this chronic study [NOAEL(HEC) = 875 mg/cu.m].

Sprague-Dawley rats (15/sex/group) were exposed to cumulative mean exposures of 0, 100, or 1481 ppm (0, 377, or 5653 mg/cu.m) toluene vapors, 6 hours/day, 5 days/week (duration-adjusted to 0, 67, and 1009 mg/cu.m, respectively) for 26 weeks (API, 1981). On weeks 9, 18, and 27, neurohistopathological examinations were
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Xylenes; CASRN 1330-20-7 (04/01/97)

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Xylenes

File On-Line 09/30/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	09/30/87
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	03/01/91

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Xylenes
CASRN -- 1330-20-7
Last Revised -- 09/30/87

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this

substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Hyperactivity, decreased body weight and increased mortality (males) Chronic Rat Gavage Study	NOAEL: 250 mg/kg/day (converted to 179 mg/kg/day) FEL: 500 mg/kg/day (converted to 357 mg/kg/day) NTP, 1986	100	1	2E+0 mg/kg/day

*Conversion Factors: Dose adjusted for gavage schedule (5\days/week).

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

NTP (National Toxicology Program). 1986. NTP Technical Report on the Toxicology and Carcinogenesis of Xylenes (mixed) (60.2% m-xylene, 13,6% p-xylene, 17.0 ethylbenzene and 9.1% 0-xylene) (CAS No. 1330-20-7) in F344/N rats and B6C3F1 mice (gavage studies). U.S. DHHS, PHS, NIH, NTP, Research Triangle Park, NC. NTP TR 327, NIH Publ. No. 86-2583.

Groups of 50 male and 50 female Fischer 344 rats and 50 male and 50 female B6C3F1 mice were given gavage doses of 0, 250, or 500 mg/kg/day (rats) and 0, 500, or 1000 mg/kg/day (mice) for 5 days/week for 103 weeks. The animals were observed for clinical signs of toxicity, body weight gain, and mortality. All animals that died or were killed at sacrifice were given gross necropsy and comprehensive histologic examinations. There was a dose-related increased mortality in male rats, and the increase was significantly greater in the high-dose group compared with controls. Although increased mortality was observed at 250 mg/kg/day, the increase was not significant. Although many of the early deaths were caused by gavage error, NTP (1986) did not rule out the possibility that the rats were resisting gavage dosing because of the behavioral effects of xylene. Mice given the high dose exhibited hyperactivity, a manifestation of CNS toxicity. There were no compound-related histopathologic lesions in any of the treated rats or mice. Therefore, the high dose is a FEL and the low dose a NOAEL.

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF -- An uncertainty factor of 100 was chosen: 10 for species-to-species extrapolation and 10 to protect sensitive individuals.

MF -- None

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

U.S. EPA (1984) reported an RfD of 0.01 mg/kg/day, based on a rat dietary NOAEL of 200 ppm or 10 mg/kg/day as defined by Bowers et al. (1982) in a 6-month study. This NOAEL was divided by an uncertainty factor of 1000. U.S. EPA (1985, 1986) noted that this study used aged rats, loss of xylene from volatilization was not controlled, only one exposure level was used, and histopathologic examination was incomplete. An RfD of 4.31 mg/day (about 0.06 mg/kg/day) based on an inhalation study (Jenkins et al., 1970) using rats, guinea pigs, monkeys, and dogs exposed to o-xylene at 3358 mg/cu.m, 8 hours/day, 5 days/ week for 6 weeks or at 337 mg/cu.m continuously for 90 days was derived by U.S. EPA (1985). Deaths in rats and monkeys, and tremors in dogs occurred at the highest dose, whereas no effects were observed in the 337 mg/cu.m continuous exposure group. The RfD based on the NTP (1986) study is preferable because it is based on a chronic exposure in two species by a relevant route of administration, and comprehensive histology was performed. Xylene is fetotoxic and teratogenic in mice at high oral doses (Nawrot and Staples, 1981; Marks et al., 1982), but the RfD as calculated should be protective of these effects.

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study -- Medium
Data Base -- Medium
RfD -- Medium

The NTP (1986) study was given a medium confidence level because it was a well-designed study in which adequately sized groups of two species were tested over a substantial portion of their lifespan, comprehensive histology was performed, and a NOAEL was defined; but clinical chemistries, blood enzymes, and urinalysis were not performed. The data base was given a medium confidence level because, although supporting data exist for mice and teratogenicity and fetotoxicity data are available with positive results at high oral doses, a LOAEL for chronic oral exposure has not been defined. Medium confidence in the RfD follows.

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- U.S. EPA, 1986, 1985, 1984

The Health and Environmental Effects Profile for Xylenes (o-, m-, p-) has received limited peer review and extensive agency-wide review, 1986.

The Drinking Water Criteria Document for Xylenes has received extensive peer and agency-wide review.

The Health Effects Assessment for Xylenes has received ECAO internal review and limited agency review.

Other EPA Documentation -- None

Agency Work Group Review -- 12/05/85, 03/19/87

Verification Date -- 03/19/87

___I.A.7. EPA CONTACTS (ORAL RfD)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX) or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Xylenes
CASRN -- 1330-20-7

Not available at this time.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Xylenes
CASRN -- 1330-20-7
Last Revised -- 03/01/91

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1

in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to human carcinogenicity.

Basis -- Orally administered technical xylene mixtures did not result in significant increases in incidences in tumor responses in rats or mice of both sexes.

___II.A.2. HUMAN CARCINOGENICITY DATA

None.

___II.A.3. ANIMAL CARCINOGENICITY DATA

Inadequate. In an NTP (1986) study, 50 male and 50 female F344/N rats were treated by gavage with mixed xylenes in corn oil (60% m-xylene, 14% p-xylene, 9% o-xylene and 17% ethylbenzene) at dosages of 0, 250 or 500 mg/kg/day, 5 days/week for 103 weeks. Similarly, 50 male and 50 female B6C3F1 mice were treated with the same xylene mixture at dosages of 0, 500 or 1000 mg/kg/day. Animals were killed and examined histologically when moribund or after 104-105 weeks. An apparent dose-related increased mortality was observed in male rats, but this difference was statistically significant for the high dose group, only. No other differences in survival between dosage groups of either sex were observed. Interstitial cell tumors of the testes could not be attributed to administration of the test compound observed in male rats (43/50 control, 38/50 low-dose and 41/49 high-dose). NTP (1986) reported that there were no significant changes in the incidence of neoplastic or nonneoplastic lesions in either the rats or mice that could be considered related to the mixed xylene treatment, and concluded that under the conditions of these 2-year gavage studies, there was "no evidence of carcinogenicity" of xylene (mixed) for rats or mice of either sex at any dosage tested.

Maltoni et al. (1985), in a limited study, reported higher incidences (compared with controls) of malignant tumors in male and female Sprague-Dawley rats treated by gavage with xylene in olive oil at 500 mg/kg/day, 4 or 5 days/week for 104 weeks. This study did not report survival rates or specific

tumor types; therefore, the results cannot be interpreted.

Berenblum (1941) reported that "undiluted" xylene applied at weekly intervals produced one tumor-bearing animal out of 40 after 25 weeks in skin-painting experiments in mice. No control groups were described. Pound (1970) reported negative results in initiation-promotion experiments with xylene as the initiator and croton oil as the promotor.

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

The frequency of sister chromatid exchanges and chromosomal aberrations were nearly identical between a group of 17 paint industry workers exposed to xylene and their respective referents (Haglund et al., 1980). In vitro, xylene caused no increase in the number of sister chromatid exchanges in human lymphocytes (Gerner-Smidt and Friedrich, 1978). Studies indicate that xylene isomers, technical grade xylene or mixed xylene are not mutagenic in tests with Salmonella typhimurium (Florin et al., 1980; NTP, 1986; Bos et al., 1981) nor in mutant reversion assays with Escherichia coli (McCarroll et al., 1981). Technical grade xylene, but not o- and m-xylene, was weakly mutagenic in Drosophila recessive lethal tests. Chromosomal aberrations were not increased in bone marrow cells of rats exposed to xylenes by inhalation (Donner et al., 1980).

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

Source Document -- U.S. EPA, 1987

The Drinking Water Criteria Document for Xylene has received Agency and external review.

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Work Group Review -- 12/02/87

Verification Date -- 12/02/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX) or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

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_VI. BIBLIOGRAPHY

Substance Name -- Xylenes
CASRN -- 1330-20-7
Last Revised -- 07/01/89

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__VI.B. INHALATION RfD REFERENCES

None

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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_VII. REVISION HISTORY

Substance Name -- Xylenes
CASRN -- 1330-20-7

Date	Section	Description
09/26/88	II.	Carcinogen summary on-line
07/01/89	I.B.	Inhalation RfD now under review
07/01/89	VI.	Bibliography on-line
03/01/91	II.D.3.	Primary contact changed
03/01/91	IV.F.1.	EPA contact changed
01/01/92	I.A.7.	Secondary contact changed
01/01/92	IV.	Regulatory actions updated

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SYNONYMS

Substance Name -- Xylenes

CASRN -- 1330-20-7
Last Revised -- 09/30/87

108-38-3
1330-20-7
2106-42-3
95-47-6
dimethylbenzene
1,2-dimethylbenzene
1,3-dimethylbenzene
1,4-dimethylbenzene
mixed xylenes
m-xylene
meta-xylene
o-xylene
ortho-xylene
p-xylene
para-xylene
Xylenes

Xylene; Downloaded 8/13/97

Xylene; Downloaded 8/13/97

ATSDR-Derived Minimal Risk Levels for Benzene

Inhalation MRL

• An MRL of 0.05 ppm has been derived for acute inhalation exposure to benzene.

An acute-duration inhalation MRL of 0.05 ppm was derived from a LOAEL value of 10 ppm for the reduced lymphocyte proliferation following mitogen stimulation in mice (Rozen et al., 1984). Male C57Bl/6 mice (7-8/group) were exposed to benzene (0-300ppm) in whole-body dynamic inhalation chambers for 6 hours/day for 6 consecutive days. Control mice were exposed to filtered, conditioned air only. Erythrocyte counts were depressed in C57Bl/6 mice only at 100 and 301 ppm. At exposures of 10 and 31 ppm, respectively, depressions of the proliferative responses of bone marrow-derived B cells and splenic T-cells occurred in C57Bl/6 mice without causing a concomitant depression in number of splenic T- or B-cells. Peripheral lymphocyte counts were depressed at all levels. No correlation was made of reduced lymphocytes with general effects. These results demonstrate that short-term inhaled benzene even at low exposure concentrations can cause reduction in certain immune associated processes.

Effects noted in study and corresponding doses:

10 ppm – Depressed peripheral lymphocytes and mitogen-induced blastogenesis of femoral B-lymphocytes. There were no adverse effects on erythrocytes.

31 ppm - Depressed mitogen-induced blastogenesis of splenic T-cells. There were no adverse effects on erythrocytes.

100 ppm – Depressed erythrocyte counts.

The ratio of the blood/gas partition coefficients was assumed to be "1." The dose was adjusted for intermittent exposure by multiplying the LOAEL (10 ppm) by 6/24 to correct for less than a full day of exposure. The resulting number ($LOAEL_{[ADJ]}$) is 2.50 ppm.

The human equivalent dose (HEC) was calculated using Formula 4-11, from Interim Methods for Development of Inhalation Reference Concentrations, EPA, 1989:

$$LOAEL_{[HEC]} (mg/m^3 \text{ or ppm}) = LOAEL_{[ADJ]} (mg/m^3 \text{ or ppm}) \times (V_A/BW)_A/V_A/BW)_H$$

where:

$LOAEL_{[HEC]}$ = the LOAEL human equivalent concentration

$LOAEL_{[ADJ]}$ = the LOAEL adjusted for duration (see above)

$(V_A/BW)_A/V_A/BW)_H$ = the ratio of the alveolar ventilation rate (mL/min or L/hr) divided by body weight (kg) of the animal species to the same parameters for humans.

Values for this ratio were taken from EPA, 1988

$(V_A)_A$ = ventilation rate for male B6C3F1 mice, subchronic, 0.053 m^3/day x 1000 L/m^3 x 1 day/24 hr = 2.208 L/hr = 2.21 L/hr

$(BW)_A$ = body weight for male B6C3F1 mice, subchronic, 0.0316 kg

$(V_A)_H$ = ventilation rate for human adult male, 20 m^3/day x 1000 l/m^3 x 1 day/24 hr = 8.33.33 L/hr = 833 L/hr

$(BW)_H$ = body weight for human adult male, 70 kg

2.50 ppm x (2.21 L/hr) / (0.316 kg) / (833 L/hr) / 70 kg = 14.7 ppm

Uncertainty factors used in the MRL derivation:

10 (for use of a LOAEL)
3 (for extrapolation from animals to humans)
10 (for human variability)

Other additional studies or pertinent information that lend support to this MRL are presented. Increased number of MN-PCEs, decreased numbers of granulopoietic stem cells (Toft et al., 1982) , lymphopenia (Cronkite et al., 1985), lymphocyte depression, increased susceptibility to bacterial infection (Rosenthal and Snyder 1985) are among the adverse hematological and immunological effects observed in several other acute-duration inhalation studies. The study by Rozen et al., (1984) shows benzene immunotoxicity (reduced mitogen-induced lymphocyte proliferation_ at a slightly lower exposure level than these other studies. In a recent study, mice exhibited a 50% decrease in the population of erythroid progenitor cells (CFU-E) after exposure to 10 ppm benzene for 5 days, 6 hours/day (Dempster and Snyder, 1991). These data support the choice of Rozen et al., 1984 as a critical study.

Agency Contact: Beth Hibbs

ATSDR-Derived Minimal Risk Levels for Naphthalene

Inhalation MRLs

• An MRL of 0.002 ppm has been derived for chronic inhalation exposure to naphthalene.

This MRL was derived from a chronic (2-year) inhalation study in mice using exposures of 0, 10, or 30 ppm (NTP 1992a). Groups of mice were exposed for 5 days per week and 6 hours per day. Body weights, clinical signs, and mortality were monitored daily. Hematological measurements were made at 14 weeks, but not thereafter; ophthalmic examinations were performed at 6-month intervals. At sacrifice, gross necropsy of all animals was performed. Histological examination of the tissues was conducted for both the control and high dose animals. Tumor incidence was evaluated in all organs.

This study identified a LOAEL of 10 ppm. A dose-related incidence of chronic inflammation of the epithelium of the nasal passages and lungs was observed. There was metaplasia of the olfactory epithelium and hyperplasia of the respiratory epithelium, but there were no treatment-related gross or histopathological lesions of the organs examined. The data suggest that the observed responses represented a respiratory inflammation and regeneration mechanism. There was an increased incidence of combined alveolar/bronchiolar adenomas and carcinomas in the lungs of the females at the high dose.

The LOAEL of 10 ppm was used for the derivation of the MRL. This concentration was normalized by adjusting for the 6-hour-per-day and 5-day-per-week exposure pattern. An uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) was applied to obtain the MRL. MRL derivation using the Human Equivalent Concentration (HEC) methodology (EPA 1989) could not be conducted because naphthalene is neither reactive nor soluble, and therefore does not fulfill the criteria necessary for HEC determination in a respiratory contaminant (EPA 1990b).

The results of the NTP (1992a) study do not suggest adverse hematological effects in exposed mice. Given that hemolytic anemia is a concern in naphthalene-exposed humans and dogs, the current findings suggest that the MRL may not have been derived in the most sensitive species, or for the most sensitive end point. Furthermore, findings of enhanced bronchiolar sensitivity in mice suggest that their response to respiratory toxins may not be representative of the response for other species.

No appropriate data were located on effects of acute- and intermediate-duration inhalation exposure in humans or animals that could be used to derive acute and intermediate MRLs for inhalation exposures.

ATSDR-Derived Minimal Risk Levels for Xylenes

An inhalation MRL of 1 ppm has been derived for an acute-duration inhalation exposure (14 days or less) to mixed xylene. This MRL is based on increased reaction times that were observed in 10 male volunteers exposed to xylenes (composition not stated) for 100 ppm for 4 hours (Dudek et al., 1990). In this study, the volunteers experienced an increased reaction time during various psycho-motor tests. An uncertainty factor of "10" was applied to the LOAEL identified in this study. An additional uncertainty factor of "10" was applied to account for inter-individual variability.

The 100 ppm is near the threshold for adverse effects as supported by Gamberale et al., (1978). In this study, no effects on reaction times were observed in 15 male volunteers exposed to xylenes at 100 or 299 ppm (12.8% para- xylene, 12.1% ortho-xylene, 54.4% meta-xylene, 20.7% ethylbenzene) through a breathing valve for 70 minutes (Gamberale et al., 1978). In eight men that exercised during the first 30 minutes of a 70 minute exposure at 299 ppm xylene, reaction time was increased and short-term memory was impaired (Gamberale et al., 1978). Effects of exposure at 10 ppm with exercise were not studied.

An MRL of 0.7 ppm has been derived for intermediate-duration inhalation exposure (15 to 364 days) to mixed xylenes. This MRL is based on the observation of reduced rotarod performance of offspring (measured on the first 3 days after birth in rats exposed to 200 ppm technical grade xylene 6 hours/day on gestation days 4 through 20 (Hass and Jakobsen, 1993). No maternal toxicity (body weight, clinical signs) or effects on reproduction and litter end-points (e.g. implantations, resorptions, fetal body weight) were observed. An uncertainty factor of "10" was applied to the LOAEL, an uncertainty factor of "3" was applied to account for interspecies differences, and an uncertainty factor of "10" was used to account for human variability.

A study by Rosengren et al (1986) in which male and female gerbils were exposed to analytical grade xylene at 0, 160, or 320 ppm continuously for 3 months followed by a 4-month exposure-free period provides further evidence that the nervous system is a target of xylene toxicity. Total glial fibrillary acid protein (GFA), a marker of astroglial cell proliferation was increased at 320 ppm. At 160 ppm, GFA was increased in the anterior cerebellar vermis, and DNA was increased in the posterior cerebellar vermis. S-100, also an astroglial marker was not altered in the 160 ppm exposures, but was increased in the frontal cerebral cortex at 320 ppm.

An MRL of 0.1 ppm has been derived for chronic exposure to mixed xylenes. This MRL is based on an increase of subjective symptoms including anxiety, forgetfulness, inability to concentrate, eye and nasal irritation, dizziness, and sore throats reported by workers exposed to xylenes for an average of 7 years at a geometric mean TWA concentration of 14 ppm (Uchida et al., 1993). Hematology, serum biochemistry (total protein, albumin, SGOT, SGPT, alkaline phosphatase, lactate dehydrogenase, leucine aminopeptidase,

amylase, BUN, creatine), and urinalysis measures did not show any differences with controls.

APPENDIX I - Background Residential Indoor Air Concentration Data for Petroleum Product Constituents

BACKGROUND RESIDENTIAL INDOOR AIR CONCENTRATION DATA FOR PETROLEUM PRODUCT CONSTITUENTS

A comprehensive search was performed to identify sources of background data for petroleum hydrocarbons in residential indoor air. This search focused on the identification of background data sources appropriate for the rural residences typical of Maine communities. This search included: telephone interviews, electronic literature searches (including the Colorado Association of Research Libraries UNCOVER data base), internet searches, a literature search of the in-house Menzie-Cura & Associates, Inc. library and a review of recent issues of *Atmospheric Environment*, *Indoor Environment*, and the *Journal of Indoor Air*. Telephone interviews were conducted with several researchers in USEPA, industry, state agencies, and academia with expertise in indoor air monitoring of volatile and semi-volatile organic compounds. In addition, an electronic version (Version 1.02) of the indoor air data base developed for U.S. EPA's National Ambient Volatile Organic Compounds (VOCs) Data Base Update was manipulated so that background levels for selected site types and compounds could be extracted.

Table I-1 summarizes the information obtained on background levels for petroleum constituents in residential indoor air. The following text discusses each of the sources of background data in greater detail. Not all of the background data found during the literature search are presented in the table or text because studies that were clearly not appropriate for Maine residences were eliminated as background data sources. These studies included those of other countries or regions of the United States (e.g., California) where fuel sources, housing properties, and typical household products are likely to be different than those in Maine. Most background data presented are from studies of U.S. homes, and special care was taken to identify background data for rural areas similar to Maine rather than areas dominated by heavy industry and other possible sources of petroleum mixtures and constituents. Although the indoor air data base includes data from a multitude of studies conducted in all parts of the country, background data from U.S. EPA's National Volatile Organic Compounds (VOCs) Data Base Update are presented because this is the most comprehensive source of indoor air data for VOCs in U.S. residences. Background data were scarce for aromatic hydrocarbons such as naphthalene and the methylnaphthalenes, and the available data for these compounds in U.S. residences are presented regardless of the study area or type. No background data were found for some petroleum constituents including the lighter aliphatic compounds (e.g., hexane, heptane, etc.).

EPA's National Volatile Organic Compounds (VOCs) Data Base Update

Several background data sources are included in the indoor air data base of U.S. EPA's National Ambient Volatile Organic Compounds (VOCs) Data Base Update. Background data in Table I-1 were either directly taken from this data base or are subsets of the data base for selected site types (e.g., only indoor residential, suburban, and urban site types and not source-dominated or workplace site types).

The indoor air data base contains over 52,000 records representing 66 VOCs measured in the indoor air of 30 cities from 16 states. Concentration data from many different study areas are included in the data base, and these data differ in their site types and quality. Nearly 90% of the indoor air data are from studies conducted in California and New Jersey, and approximately 98% were collected between 1981 to 1984. Greater than 95% of the indoor air data are from time-integrated samples with sampling periods ranging from 1 to 24 hours.

Shah and Singh (1988)

Background levels for benzene, ethylbenzene, toluene, o-xylene, p-xylene, 1,2,4-trimethylbenzene, 1,3,5-trimethylbenzene, n-decane, n-undecane, n-tridecane, and n-tetradecane were obtained from Shah and Singh (1988). Shah and Singh (1988) reported summary statistics for a number of VOCs from the entire indoor air data base included in U.S. EPA's National Ambient Volatile Organic Compounds (VOCs) Data Base Update. They note that some ambient data are also in the indoor air data base because these data were included in indoor references as part of the study. Shah and Singh (1988) did not separate data by site type in their summary table, so this table includes data from a variety of very different site types including remote, rural, suburban, urban, source-dominated, indoor residential, workplace, and personal exposures. Due to some high values, their arithmetic average may be skewed high, and Shah and Singh (1988) report that the median value may better represent the data set than the arithmetic average.

Massachusetts Department of Environmental Protection (1991)

The Massachusetts Department of Environmental Protection (MADEP, 1991) determined representative background indoor air concentrations for benzene, toluene, and total xylenes in Massachusetts indoor air using U.S. EPA's National Ambient Volatile Organic Compounds (VOCs) Data Base Update. MADEP worked with the indoor air data base to select only data for site types that are more representative of residential indoor air. Briefly, MADEP linked chemical files with the sampling location files and only extracted records corresponding to suburban, urban, and indoor residential exposures. These data were linked to the analytical parameters files, and chemicals that were not detected were assigned a concentration equal to one-half the reported method quantitation limit. Because the data base contains data for the individual xylene isomers and not for total xylenes, xylenes were treated as a special case. The m-xylene and p-xylene files were nearly identical; therefore, it was assumed that these data represent the sum of the two isomers and that the use of both data files would be redundant. Lognormal distributions were then fit to concentration data for o-xylene and p-xylene only, and statistical parameters from these distributions were used in a Monte Carlo simulation to predict the probable distribution of total xylenes given the measured data for the individual isomers.

The 50th and 95th percentiles are presented from the MADEP background values for benzene, toluene, and xylenes in **Table X**.

Version 1.02 Data base Manipulation

Background levels of benzene, ethylbenzene, toluene, o-xylene, m+p-xylene, 1,2,4-trimethylbenzene, 1,3,5-trimethylbenzene, n-decane, n-undecane, n-dodecane, n-tridecane, n-tetradecane, and 2-methylnaphthalene were determined using a subset of the indoor air data base. Version 1.02 (1987) of the indoor air data base was manipulated to obtain background data for selected petroleum hydrocarbons in residential indoor air. Version 1.02 differs slightly from the 1988 Data Base Update because a small amount of 1988 data were added. Data base files of concentration data, sampling locations, and analytical parameters (e.g., method quantitation limits) were linked in Microsoft Access and indoor air data for selected petroleum hydrocarbons and site types (suburban, urban, and indoor residential) were exported to Microsoft Excel spreadsheets. Concentration data for several site types, including source-dominated and indoor workplace, were not used because these data are not representative of Maine residential indoor air. One-half the method quantitation limit was entered for cases where compounds were not detected and a concentration of zero was reported. Summary statistics (e.g., arithmetic average, range of detected values, and percentile values) were generated for the petroleum compounds of interest.

Because we followed a similar method to that of MADEP (1991) to select the data in the indoor air data base that are most appropriate for residential indoor air, it was expected that similar data would be obtained for benzene and toluene where MADEP background levels are available. The percentiles for toluene are identical to those determined by MADEP (1991). The MADEP percentiles for benzene are approximately twice those determined using Version 1.02 of the indoor air data base, indicating that either new benzene data were added to the data base update or data were either deleted or changed. No comparison between xylenes data was made because MADEP (1991) reported background levels for total xylenes and the data base only contains data for the individual xylene isomers.

Vermont Department of Health (1993)

Background data for a number of VOCs are available in the Vermont Indoor Air Ambient Quality (VIAAQ) Survey. These compounds include benzene, ethylbenzene, m+p-xylene, o-xylene, and toluene. This study was organized in late 1991 and conducted between December 1991 and December 1992 to provide background data for VOCs which are more representative of rural areas with few or no industrial VOC sources than the U.S. EPA TEAM Study data. The purpose of the Vermont study was to establish a baseline for indoor air VOCs for remote residences where building supply and home product/lifestyle sources are larger contributors to indoor air quality than outdoor contaminant sources.

Background data were taken from a summary data table provided in the Vermont Study. Minimum, average, median, and maximum results are available for over 200 analytical samples. Based on a phone conversation with Dr. William Bress, the project manager for this study, some caution is warranted when using the data for VOCs including the BTEX compounds because the study had poor reproducibility among replicate samples.

Stolwijk (1989)

Background levels for benzene, ethylbenzene, toluene, o-xylene, m+p-xylene, 1,2,4-trimethylbenzene, 1,3,5-trimethylbenzene, n-decane, n-undecane, n-dodecane, n-tridecane, n-tetradecane, and naphthalene were obtained from Stolwijk (1989). This study consolidated data on indoor air concentration distributions from residential indoor air quality studies conducted in the Federal Republic of Germany, Italy, the Netherlands, and the U.S. These studies were conducted with different study objectives and sampling conditions. Sampling periods ranged from 2 to 12 hours for the U.S. study data to 2 weeks for the German study data. The study sample sizes ranged from a low of 15 homes for the Italian study data to a high of 500 homes for the German study data.

Stolwijk (1990) reports both mean values (if they could be reasonably calculated) and percentiles for indoor air concentration data. Because this consolidated dataset includes data collected for different sampling periods and conditions, Stolwijk (1989) cautions that the reported concentration distributions are for the "normal" or average situation and as such have a range of uncertainty of about 50%. The consolidated dataset includes data for hundred of buildings and thus only gives a probability of VOC concentrations that might be present in other buildings. However, higher concentrations may exist in some buildings where special products or materials are present or when permanent sources are within or near the building. Concentrations in many buildings may fall at the low end of the reported concentration distributions.

EPA's Total Exposure Assessment Method (TEAM) Studies

Background data for benzene, ethylbenzene, o-xylene, and m+p-xylene were obtained from U.S. EPA's Total Exposure Assessment Method (TEAM) Studies. These data were taken from nighttime personal exposure data for studies conducted in Greensboro, North Carolina and Devils Lake, North Dakota.

U.S. EPA's Total Exposure Assessment Method (TEAM) Studies were conducted in 8 U.S. cities between 1980 and 1987. Exposures of approximately 800 persons to 25 VOCs were evaluated in these studies. The majority of these studies took place in medium-sized cities in areas of intensive chemical manufacturing and petroleum refining. The studies in Greensboro and Devils Lake were the only study areas that included rural areas without known VOC sources. Personal exposures to VOCs were measured, and daytime and nighttime sampling exposures were separated measured using the compact personal

samplers. Because nighttime personal samplers were kept at the bedside of the sleeping study participant, these data are assumed to adequately represent indoor air quality.

Weighted summary statistics for the overnight personal air samples for both Greensboro and Devils Lake were obtained from Wallace (1991). No data for benzene were reported in the Devils Lake study based on quality assurance results.

Chuang *et al*. (1991)

Background data for naphthalene was obtained from Chuang *et al*. (1991). In this study, the indoor air of eight homes in Columbus, Ohio were sampled during the winter of 1986/1987. These homes were selected for indoor air assessment on the basis of several characteristics including: electric/gas heating system, electric/gas cooking appliances, and the absence/presence of environmental tobacco smoke (ETS). Time-integrated indoor air samples were collected over two consecutive 8-hour periods in the kitchens and living room areas of the houses for a total of 16 samples. Both gas- and particulate-phase polycyclic aromatic hydrocarbons (PAHs) were collected by indoor air samplers. Naphthalene was the most abundant PAH detected in indoor air, and higher concentrations were detected in homes where there were smokers and gas heating systems.

Offerman *et al*. (1991)

Background data for biphenyl, naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene were obtained from Offerman *et al*. (1991). This study reported the results of indoor air quality monitoring for both gas- and particulate-phase PAHs in residential homes and office buildings in northern California. Study homes included those without active combustion sources and with gas stoves, wood stoves, and cigarette smoking.

Background data taken from this study are for the residential indoor air samples only. Both daytime and nighttime measurements were taken from the living/dining room areas of the three study homes, and two consecutive 12-hour time-integrated samples were collected over both the daytime and nighttime time periods. Including duplicate samples, a total of 26 indoor air samples were collected from the three single-family residences. Minimum, maximum, and arithmetic average concentrations for biphenyl, naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene in these 26 samples are presented in the table as background data.

(placeholder for table I – 9 pages)

APPENDIX J - Odor Thresholds for Selected Petroleum Products and Constituents

Table J-1
Odor Thresholds of Petroleum Products and Constituents

Compound	Odor Thresholds[a,b] (ppm)	Odor Thresholds[a,b] (mg/m^3)	Source
Petroleum Products			
Gasoline	0.25	NC	ATSDR Profile (1995)
Fuel Oil No. 2	0.5 - 0.7	NC	Likely range[c]
Kerosene	0.082 - 1	NC	ATSDR Profile (1995)
BTEX Compounds			
Benzene	1.4-56	4.5-180	USEPA (1992)
Toluene	2.1-37	8-140	USEPA (1992)
Ethylbenzene	0.5	2	ATSDR Profile (1991)
p-Xylene	0.081-23	0.35-100	USEPA (1992)
m-Xylene	0.081-23	0.35-100	USEPA (1992)
Mixed Xylenes	0.10	0.44	ATSDR Profile (1991)
Other Alkylbenzene Compounds			
1,3,5-Trimethylbenzene	0.91	4.5	USEPA (1992)
Alkanes			
Cyclohexane	10-59	35.6-202	ASTM (1978)
n-Nonane	11-650	60-3400	USEPA (1992)
Naphthalenes			
2-Methylnaphthalene	0.012	0.068	USEPA (1992)
Naphthalene	0.29-7.3	1.5-38	USEPA (1992)
1-Methylnaphthalene	0.009-0.02	0.05-0.1	USEPA (1992)

Notes:

[a] Odor thresholds for petroleum products were available in units of ppm. These values were not converted to mg/m3 due to uncertainty regarding the molecular weights of these mixtures.

[b] Odor thresholds for petroleum constituents were available in units of mg/m^3. These values were converted to units of ppm assuming standard pressure and temperature.

[c] Extrapolated range based on odor thresholds of Fuel Oil No. 1-D (Diesel Oil No. 1) and Fuel Oil No. 4,

APPENDIX K - Occupational and Spacecraft Guidelines for Petroleum Constituents

Table K-1
Comparison Between Occupational and Spacecraft Guidelines

Compound	Recommended Exposure Limits[a]		Permissable Exposure Limit[a]		Threshold Limit Value[b]		Spacecraft Maximum Allowable Concentrations[c] 7 day duration		Spacecraft Maximum Allowable Concentrations[c] 180 day duration	
	ppm	mg/m^3	ppm	mg/m^3	ppm	mg/m^3	ppm	mg/m^3	ppm	mg/m^3
benzene	0.1	0.32	1	3.2	10	32	0.5	1.5	0.07	0.2
ethylbenzene	100	435	100	435	100	434	30	130	12	50
n-hexane	50	180	500	1800	50	176	NA	NA	NA	NA
n-nonane	200	1050	NA	NA	200	1050	NA	NA	NA	NA
naphthalene	10	50	10	50	10	52	NA	NA	NA	NA
toluene	100	375	200	1050	50	188	50	217	50	217
xylenes	100	435	100	435	100	434	16	60	16	60

Source:
[a] "NIOSH: Pocket Guide to Chemical Hazards", U.S. Department of Health and Human Serivces, June 1994 plus the "pen and ink changes" as of 11/6/96
[b] "Threshold Limit Values for Chemical Substances and Physical Agents Biological Exposure Indices", American Conference of Governmental Industrial Hygenists, 1996.
[c] "Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants," Volumes 1 and 2. National Academy Press. Washington, D.C. 1996.
NA = Not Available